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RETROPUBIC PROSTATECTOMY*

GEORGE AUSTEN, JR., M.D.,† AND WILLIAM C. QUINBY, M.D.‡

BOSTON

UNTIL recently time and experience had accepted as satisfactory three principal operative approaches to the prostate: perineal prostatectomy, suprapubic transvesical prostatectomy and transurethral prostatectomy. No single one of these procedures alone is applicable for the treatment of every type of prostatic obstruction. In spite of the contention of surgeons who are strong proponents of one method to the exclusion of the others, it seems fair to say that each of these procedures has certain indications and contraindications, as well as certain limitations and disadvantages, and that each is attended by various technical difficulties that may render the results of operation unsatisfactory. Therefore, when a new and logical method of treatment is proposed, which apparently produces good results in intelligent hands, the progressive surgeon must examine it carefully.

In 1945 Millin,[1] of London, presented his initial report of "a new extravesical technique" of prostatectomy, a suprapubic operation for nonmalignant lesions of the prostate to which he applied the name "retropubic prostatectomy." Although Millin considered his operation original, he noted that a somewhat similar suprapubic extravesical approach to the prostate had been made and reported by others. He referred to the reports of van Stockum[2] in 1909 and of Jacobs and Casper[3] in 1933. In both communications there were certain variations in the technic of actual enucleation of the obstructing lobes and closure of the capsule that differed distinctly from the operation described by Millin. He also added that in 1924 Maier[4] reported 4 cases in which the gland was removed by an inguinal extravesical route. However, a review of the literature demonstrates that Millin's report is the first record of any appreciable series of cases treated consistently in this fashion, and it is fair to allow his claim to the originality and development of the technic that he described.

In his initial publication Millin reported the results obtained in 20 patients with benign prostatic disease who were operated upon by this method; 13 patients had generalized hypertrophy, 2 had fibrous glands with sclerotic bladder neck, 1 had calculous disease, 2 had pure lateral-lobe hypertrophy, 1 had generalized hypertrophy associated with a prostatic abscess, and 1 had post-prostatectomy scarring of the prostatic urethra. There were no postoperative deaths, and complications were few. There were 2 cases of minor delayed bleeding, both in patients who had had grossly infected bladders before operation, which was easily controlled by the use of an inlying catheter for forty-eight hours. No cases of immediate hemorrhage, gross infection, pyelonephritis or renal failure were encountered. A femoral-vein thrombosis developed in 1 case, and an abscess of the testis in another. In only 3 cases was there suprapubic leakage of urine after removal of the urethral catheter on the sixth or seventh postoperative day, and in these cases it was felt that this occurrence was the result of initial faulty adjustment of the catheter. Concerning the long-term follow-up results, Millin believed that it was too early to pass a verdict on the incidence of post-prostatectomy obstruction, but subsequent reports from his clinic[5–7] have shown that postoperative contracture of the vesical neck occurs occasionally. For that reason he has made a modification in his original technic, which is described below. However, in summarizing the results in his first 20 cases, Millin stated that "The post-operative comfort has to be seen to be believed." There was apparently very little bleeding into the bladder, catheter irrigations were rarely necessary, and "bladder spasms, so common after the classical prostatectomy," were "absent or minimal."

During the year and a half since the publication of his first report of this new operation, Millin has presented the results obtained by this technic in increasingly larger series of 85 cases[5] and 184 cases.[6] Of his 85 cases, 75 were done in a one-stage and

*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.
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10 in a two-stage procedure. In the series of 184 cases, approximately 4 per cent had been two-stage procedures. Millin believed that in the future these might form a larger proportion — perhaps 10 per cent. He found no particular difficulty in carrying out a second-stage retropubic prostatectomy when a previous cystostomy had been performed. Although the morbidity and mortality rate for the total series of 184 cases was not recorded, he noted that among his first 85 cases he had had 4 cases of minor hemorrhage and 5 of bladder-neck obstruction due to postoperative stricture or contracture of the vesical outlet. There had been 4 deaths — 2 from pyelonephritis, and 2 from cardiac failure. Since these reports Millin has performed retropubic prostatectomy in more than 400 cases, with a mortality rate of approximately 4 per cent. His experiences with the procedure in this larger group of cases were discussed at the 1947 meeting of the American Urological Association. The operation has been described in the book that he published recently.[7] As a result of his experience to date, he considered retropubic prostatectomy to be "the procedure of choice in every case affording a reasonable operative risk, except for those cases which presented fibrosis and which should have endoscopic resection."

Since Millin's original communication, reports of the results obtained by this operation have been published by other authors in the British medical literature. Although no specific mention has been made of the type of obstruction for which the operation was performed, in the majority of recorded cases the patients apparently had simple benign hypertrophy of the prostate. Series numbering from 3[8] to 63 cases[9] are mentioned. With one exception,[10] all authorities seemed to believe that the procedure had great merit, primarily because of its direct approach to the prostate, avoidance of trauma to the bladder, easy postoperative course with absence of persistent suprapubic leakage of urine, and good functional results. Although the number of patients operated upon by Millin's technic is still relatively small, the death rate and frequency of occurrence of complications in the published cases seem to confirm the optimism of the authors. Jacobs,[9, 11] in a series of 63 cases, had 5 deaths (a mortality of 7.9 per cent), only 2 of which could be attributed to complications directly attendant upon the operation itself. Complications were few and of minor importance. Riches,[12] in commenting upon his results in a series of 40 cases, recorded no deaths. He had 4 postoperative strictures at the vesical neck and 1 case of osteitis pubis. Galbraith[13] noted in his series of 23 cases only 2 minor complications, and Ward[14, 15] reported good results in 7 cases. The principal technical difficulties of the operation mentioned were inability to control bleeding from the periprostatic veins and the possible difficulty of enucleation where there was much prevesical fat, a deep pelvis and a small prostate. Although no cases of carcinoma of the prostate operated upon by this technic have been noted in the literature, it is reported that Millin himself has performed total prostatectomy through a suprapubic prevesical approach and that the complete removal of the gland was as readily accomplished as simple removal of hypertrophied lobes and fibrosed nodules.

After reviewing the published reports of Millin and others, and as a result of our own experience in attacking the prostate by this approach, we believe that the operation of retropubic prostatectomy, in comparison with the three standard methods of prostatectomy, has the following definite features to recommend it.

The anatomy of the approach is simple and direct, and it presents no important structures that need be sacrificed or organs whose function need be endangered. The dangers of the perineal approach — namely, injury to the external sphincter and rectum — are avoided, and since the procedure is an extravesical one, neither the bladder nor the vesical neck is exposed to the trauma attendant upon the suprapubic transvesical approach.

The exposure of the prostate is excellent, and the entire gland, except for its posterior surface, may be clearly visualized and palpated from the level of the apex below to the level of the bladder neck above.

After enucleation of the hypertrophied lobes, the entire prostatic cavity and vesical outlet may be exposed and examined far more completely than in either of the other standard types of open prostatectomy. Particularly advantageous is the easy control of bleeding, especially that which is prone to occur beneath the posterior vesical lip, and the accessibility of the bladder neck to inspection and any corrective plastic procedures that are found to be necessary. Since the latter structure is not unduly torn or traumatized, as inevitably occurs in the transvesical operation, the intact outlet with its sphincteric action may act immediately after operation as a barrier to the retrograde ooze of blood from the closed prostatic cavity into the bladder and thus prevent to a certain degree much of the postoperative vesical spasm and discomfort often associated with the other types of prostatectomy. Although the exposure is unusually satisfactory, we believe that the Millin operation affords no particular advantage over transurethral resection for the treatment of patients with contracture or sclerosis of the bladder neck except when a plastic procedure is also required.

Reconstruction and repair of the prostatic urethra, with watertight closure of the prostatic

capsule, is easier by this approach than by the other types of prostatectomy. Provided closure of the capsule and fascia is accurately performed in layers and the inlying catheter is properly adjusted, leakage of urine, which is not infrequent after either perineal or suprapubic transvesical prostatectomy, should rarely occur.

If hemostasis and closure are complete, and urinary leakage avoided, pelvic sepsis is greatly minimized.

In our experience, as in that of others, the most striking feature of the operation is the easy postoperative course for the patient and hospital staff alike. There is very little bleeding into the bladder, and in the majority of cases the urine is clear within twenty-four to thirty-six hours. As a result, frequent irrigations are rarely necessary for more than a few hours after operation and may generally be discontinued except for several cleansing washings daily within twelve to twenty-four hours. There is a variable amount of serosanguineous drainage from the lower angle of the abdominal wound, which may require a change of dressing every eight to ten hours for the first twenty-four to forty-eight hours postoperatively, but thereafter drainage is slight or absent and the incision is usually completely healed in seven to ten days. With no accumulation of blood clots in the bladder and with a dry suprapubic wound after the first few days, the patient has a remarkably comfortable convalescence with little local pain and generally no bladder spasm whatsoever. The use of a small No. 20 to 22 Fr. Foley balloon catheter minimizes the occurrence of urethritis and any resulting local discomfort. As a rule, the patient is urged to be out of bed on the first day after operation and is ambulatory on the second day.

After removal of the urethral catheter on the fifth to the seventh postoperative day, the patient voids easily and freely, rarely complains of any dysuria and has excellent control of urination. In only 1 case in our series has there been any incontinence, and this was of short duration.

Postoperative urinary sepsis is minimal, and, in contrast to the findings in patients who have undergone transurethral or suprapubic transvesical prostatectomy, a good proportion of cases show a grossly clear urine with little microscopical evidence of infection in the sediment.

In the majority of cases, discharge from the hospital may be accomplished in ten to fourteen days.

In spite of the advantages offered by Millin's operation, the procedure has the following disadvantages, which, at this stage of its development, may be more apparent than real:

The approach may require some time and effort in the adipose patient or in one with an unusually deep and narrow pelvis where the prostate is situated deep at the bottom of a funnel.

In cases in which a previous open cystostomy had been performed, the retropubic approach would probably entail more dissection and trauma than the transvesical method and would thus be less desirable than the latter for a second-stage prostatectomy. We have had no experience with this type of case.

The control of bleeding from the larger vessels in the endopelvic fascia is not always readily accomplished. However, this difficulty is a minor one and should be overcome as the surgeon becomes better acquainted with the operation and the anatomic variations that occur in this region. Hemostasis at this point is greatly facilitated by the use of proper instruments, such as a long-handled needle holder or the boomerang needle, as well as by knowledge of exactly where and how deep to place the transfixing ligatures.

Since the large central vein running longitudinally across the anterior surface of the prostate is in direct communication with the deep dorsal vein of the penis, it has been suggested that ligation and division of this vessel might be followed by edema of the penis. Mild and temporary edema of the penis, which subsided in two or three days, occurred in only 1 case in our series. A similar occurrence of temporary duration has been reported in a few cases by other authors. In view of the extensive anastomotic communications between the veins of the penis and the pudendal plexus, it is difficult to believe that any serious permanent vascular complications of this sort would occur.

When enlargement of the lateral lobes is slight, or when hypertrophy is confined to a subtrigonal or intravesical median lobe, it may be difficult to reach the obstructing tissue with ease. In such cases the outline of the presenting portion of the prostate is hard to define clearly by palpation, and the gland is so mobile that it tends to fall away from the dissecting finger or instrument. This is a disadvantage when one is dealing with the small sclerotic gland or fibrosed vesical neck unless one resorts to the use of a finger in the rectum or a rectal balloon to elevate the gland.

In cases with hypertrophy of the median lobe only, particularly when the enlargement is chiefly intravesical or subtrigonal and is accompanied by excessive fibrosis, enucleation is likely to traumatize and tear the bladder neck. As a result, one of the purposes of the operation — that is, preservation of an intact vesical outlet — is defeated. However, in our experience, this complication has not interfered with a good func-

tional result. When the bladder neck has been torn, one or more simple plicating sutures of catgut will satisfactorily restore the normal anatomy of the outlet.

The approach does not afford adequate visualization of, or ready access to, the posterior aspect of the prostate or its apex in the region of the membranous urethra. Therefore, in cases of early prostatic carcinoma, in which total prostatectomy is indicated, it is our opinion that the prevesical route is much less advantageous than the perineal.

In summarizing the features of the retropubic operation as already outlined, we believe that the Millin technic is particularly suited for treatment of the following types of prostatic disease: benign hypertrophy of the lateral lobes or of lateral lobes and median lobe combined; benign hypertrophy of the median or subtrigonal lobes when intravesical extension is not marked; and calculous disease of the prostate, particularly when associated with benign hypertrophy. With increasing experience and future developments in technic, this approach may also prove to be a good method of performing plastic procedures in the prostatic urethra and at the bladder outlet.

At present we believe that the Millin operation is not indicated for the treatment of patients with obstruction due to sclerosis of the vesical outlet and prostatic fibrosis. In such cases transurethral resection is the preferred procedure. Likewise, in cases of prostatic obstruction associated with disease of the bladder in which surgical therapy of both lesions is required, it is our opinion that some method other than the retropubic approach is indicated. In this category may be grouped patients with prostatic obstruction who also have a vesical tumor, large vesical calculi, a poorly draining diverticulum with or without tumor and any other vesical lesion necessitating surgery. Although small bladder calculi may be removed by the Millin approach without injury to the vesical outlet, stones larger than the intact outlet should be extracted transvesically unless they can be easily crushed and removed transurethrally. For treatment of simple calculous disease or abscess of the prostate without associated benign hypertrophy, the perineal approach is considered preferable to the retropubic one. And finally, for the reasons mentioned above, we believe that the retropubic operation is not suited to the treatment of early carcinoma of the prostate.

The actual details of the technic of the retropubic operation, as described by Millin and modified by ourselves and others, will be outlined briefly. After induction of anesthesia, the patient is placed supine on the operating table and in slight Trendelenburg position. If preoperative urethral drainage has been carried out, the bladder is completely emptied, and the catheter is removed. If the patient has not been on constant urethral drainage, catheterization is performed, and the bladder is evacuated of all residual urine. Failure to comply with this routine immediately prior to operation results in a distended bladder during the operation. As a consequence, the operative field is limited, it is more difficult to expose the prostate adequately, and when the prostatic urethra is opened there is much unnecessary leakage of urine, which not only delays the procedure but also enhances the likelihood of postoperative pelvic sepsis. Subsequent to catheterization, the abdomen, pubes and genitalia are prepared and draped. The penis is covered with a loose sterile towel. A midline suprapubic incision is made, extending from low over the pubis upward for a distance of 10 to 12 cm., depending largely upon the thickness of the abdominal wall and the depth of the bony pelvis. It should be stressed that the lower angle of the abdominal incision must extend well down over the pubis to afford adequate exposure after the self-retaining retractor has been inserted. If the incision is not carried low enough, it later becomes necessary to use an anterior retractor over the pubis to prevent the abdominal wall from obscuring visualization of the depths of the wound. Such a retractor hinders rather than aids the deep dissection. The aponeurosis of the recti is incised longitudinally, the recti are separated in the midline, and the prevesical space is exposed. The prevesical fat and peritoneal fold are then swept upward with finger dissection to expose the anterior surface of the bladder. A self-retaining Balfour retractor with medium-sized curved lateral blades is introduced to keep the edges of the abdominal incision widely separated. Millin advocates the use of a retractor with a self-retaining posterior blade to press the bladder upward and backward, but we have found that by using a broad, malleable ribbon retractor, which can be manipulated by an assistant as desired, the exposure is even better. In contrast to the impression of many surgeons that the prostate lies well down beneath the pubic arch, it is surprising how easily and clearly the prostate is exposed in its entirety by this approach. If difficulty in exposure is encountered, gentle upward traction on the bladder accompanied by finger dissection of the fatty tissue surrounding the bladder neck and prostate will bring the entire gland and vesical neck into clear view (Fig. 1).

A variable amount of fatty and areolar tissue lies deep in the retropubic or prevesical space. This is loosely attached to the bladder neck as well as to the anterior and lateral surfaces of the endopelvic fascia which in turn tightly encloses the prostate. By gentle blunt dissection with either a finger or a small swab on the end of a hemostat this tissue may be easily displaced without bleeding except

in an occasional case in which a superficial longitudinal tributary of the pudendal plexus may necessitate ligation. A medium-sized swab or gauze pack, as suggested by Millin, may be pushed into the lateral recess on each side of the prostate to keep the loose fat out of the field as well as to immobilize the gland and control minor venous ooze. The lower portion of the bladder, the vesical neck, and the prostate are clearly exposed, and the distribution of the veins coursing longitudinally across the anterior and lateral aspects of the gland may be noted. These vessels, the prostatic veins, form the prostatic plexus. They lie partly in the fascial sheath of the prostate, the prevesical or endopelvic fascia, and partly between the sheath and the true prostatic capsule. They communicate laterally with the pudendal and vesical plexuses, which in turn drain into the vesical and hypogastric veins. The prostatic veins, as visualized through the retropubic approach, divide themselves into three principal groups, a central longitudinal one whose chief tributary is the deep dorsal vein of the penis and a lateral group on each side of the gland. Anatomic variations are frequent. We have found with increasing experience that the lateral groups of veins generally need not be disturbed. If they are torn during the course of later manipulations, it is a relatively easy matter to clamp them with Kocher clamps and then either transfix and

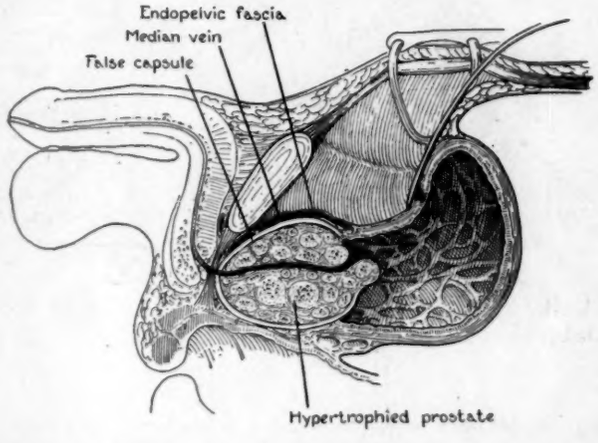

FIGURE 1. *Median Sagittal Section of the Male Pelvis Showing the Route of Approach through the Prevesical Space and the Anatomic Relations of the Bladder, Prostate, Pubic Bone and Triangular Ligament.*

The position of the median prostatic vein between the endopelvic fascia and the true capsule is illustrated.

ligate the ends or fulgurate them with the diathermy. The central vein, on the other hand, lies directly in the path of the capsular incision and must be divided. Prompt and effective control of bleeding from this vessel has been our most harassing problem in the retropubic approach, and we believe that it is best handled in either one of two fashions. The vessel may be doubly transfixed with deep bites of the needle, ligated and then divided — a boomerang needle or a short, strong, curved needle with a long-handled holder may be used. Or the incision through the endopelvic fascia may be made at once, and the bleeding ends

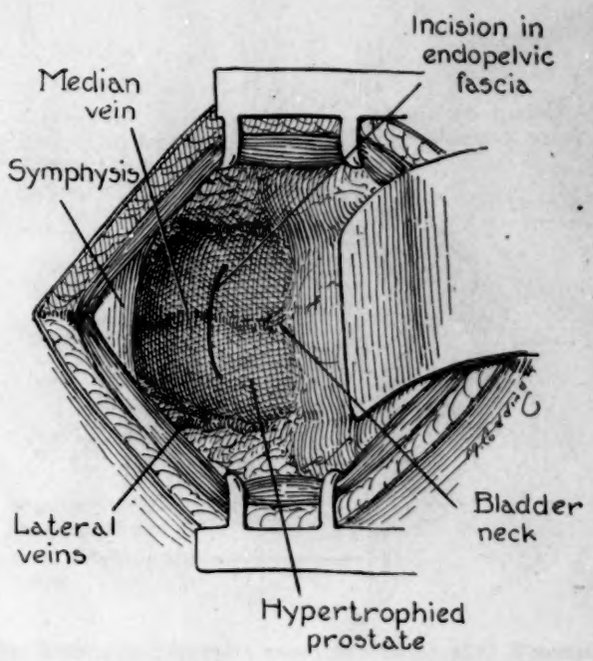

FIGURE 2. *Suprapubic View of the Prevesical Space, Showing the Exposure of the Bladder Neck, Prostate and Three Principal Groups of Prostatic Veins, and Illustrating the Site of Incision through the Endopelvic Fascia and True Prostatic Capsule.*

of the vessel thus exposed are clamped with Kocher hemostats and ligated or fulgurated with diathermy. We prefer the former method and have found that in general transfixion and ligation are preferable to the fulgurating current for control of bleeding from this large vessel. Other smaller bleeders can be adequately controlled by diathermy. A 2-cm. to 3-cm. curved transverse incision, convex downward and approximately 1.0 to 1.5 cm. distal to the junction of prostate and bladder neck, is made through the endopelvic fascia and true prostatic capsule with a long-handled No. 15 Bard–Parker blade (Fig. 2). Suction is maintained to keep the field dry, and any bleeding vessels in the lips of the capsular incision are grasped with Kocher clamps. With these clamps as tractors the upper and lower flaps are undermined with long dissecting scissors, the upper flap for a distance of not more than 0.5 cm., depending upon the proximity of the incision to the vesical neck, and the lower one for a distance of 1 cm. or more, at least for a depth sufficient to expose the lower portion of the gland

except at its very apex. It is often unnecessary to undermine the upper flap at all, since it tends to retract spontaneously during the course of later enucleation. Either the Kocher clamps are touched with the fulgurating current or the vessels are transfixed and ligated, and the hemostats are then removed. One or two traction sutures of silk are placed in the edge of the upper and lower flaps,

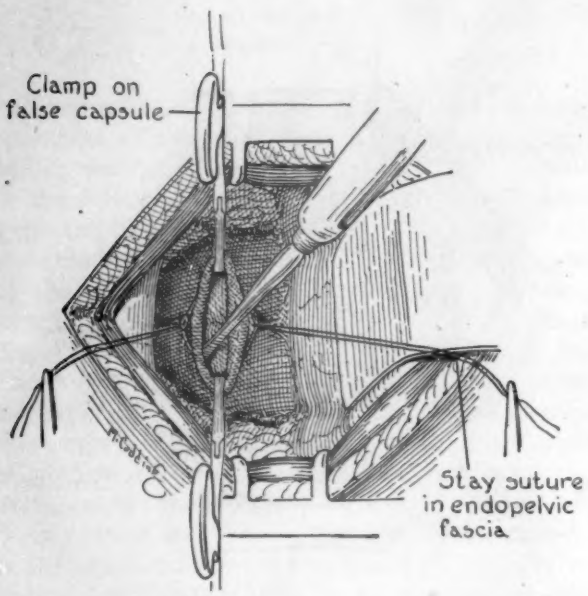

FIGURE 3. *The Upper and Lower Flaps of Endopelvic Fascia Have Been Elevated with Traction Sutures, and the Hypertrophied Lateral Lobes Are Exposed through an Inverted V Incision in the False Capsule.*

and the operator should be able to expose the anterior and part of the lateral aspects of the false capsule for a vertical distance of approximately 2 or 3 cm.

An inverted V incision, with the apex of the V pointing distally in the midline, is made in the false capsule and is carried down to expose the hypertrophied lateral lobes, which are easily recognized by the grayish-white, whorled appearance of the adenomas. If these structures are only slightly enlarged, it is sometimes wiser to continue the incision down into the prostatic urethra. By this means, the line of demarcation between false capsule and adenomas can frequently be more easily recognized. The V-shaped flap is elevated, and a diamond or lozenge-shaped space is opened into which the tip of a finger can be readily inserted. The lateral angles of this incision are grasped with Allis clamps to bring the prostate up toward the operator and at the same time to immobilize it during the course of subsequent enucleation. With a blunt spatula or long curved dissecting scissors the lower lateral margin of the right or left lateral lobe is freed from the false capsule toward the apex of the gland, and a similar procedure is carried out on the opposite side either then or after one lateral lobe has been more completely exposed (Fig. 3). The enucleation of one and then the other lateral lobe is continued with the finger. We have found that the actual digital enucleation is greatly aided by temporary removal of the bladder retractor. The lateral blades of the self-retaining retractor are not disturbed. The lateral lobes having been freed at the apex from below upward, the finger is passed across the midline beneath the distal third of the prostatic urethra, and that structure is then cut with a scalpel or scissors. The severed distal end of the prostatic urethra will retract without bleeding. Lobe forceps are applied to the presenting apical portions of the lateral lobes, and by continued traction and finger dissection posterolaterally from below upward, the lateral lobes, as well as the median lobe when present, are brought up into the capsular wound, being now attached only in the region of the bladder neck (Fig. 4). The fibrovascular pedicle of each lateral lobe is clamped with a Kocher hemostat, and the adenomas are detached distal to the clamp with scissors or

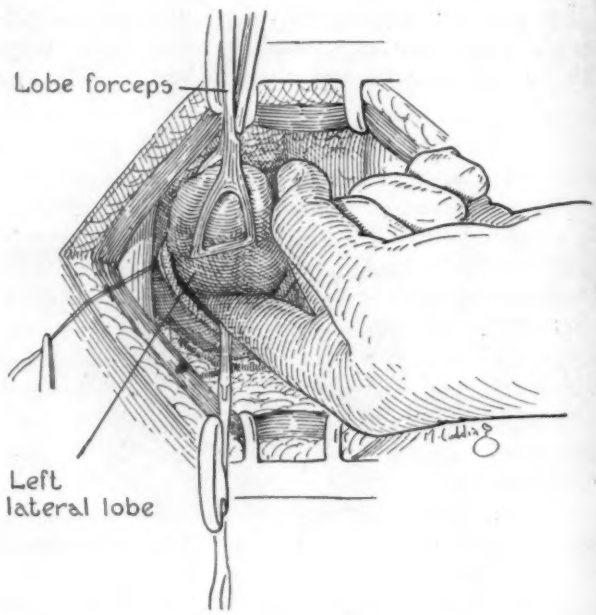

FIGURE 4. *The Apexes of the Lateral Lobes Have Been Freed from the Capsule Distally and Posterolaterally, Have Been Grasped with Lobe Forceps and Are Then Enucleated from Below Upward.*

the scalpel. The median lobe is now enucleated digitally or by sharp dissection from below and behind the floor of the vesical outlet (Fig. 5). Any ragged ends of mucous membrane of the proximal urethra or posterior vesical lip are removed cleanly at the bladder outlet with scissors. The pedicles of the lateral lobes are ligated with No. 00 plain catgut, and the hemostats are removed.

In cases in which one is dealing with a sclerotic bladder neck or fibrosed gland or in which the hypertrophy of the lobes is minimal, the technic described above is modified to a certain extent. Since the prostate is small and mobile in such cases, finger enucleation is difficult because the gland tends to fall away from the operator. However, by the application of Allis clamps at the four angles of the capsular incision and by upward lifting of the prostate, the gland is immobilized so that sharp dissection of either small lobes or fibrosed tissue may be performed with relative ease. As suggested above, the use of a rectal balloon or a finger in the rectum to push the prostate upward and forward is of benefit in cases such as these.

The bladder retractor is now replaced, and by traction on Allis forceps secured at the angles of the capsular incision the prostatic bed and vesical outlet are completely exposed to direct inspection. Any bleeders may be seen with ease and are ligated or fulgurated with the coagulating current. By placing an Allis forceps on the edge of the posterior vesical lip, one may lift up the bladder neck and readily control any bleeding in this region, particularly that which may occur from the prostatic arteries in the posterolateral recesses of the prostatic cavity. Furthermore, this exposure allows one to see and remove any tags or small nodules that might otherwise be overlooked. Hemostasis having been completed, the finger is inserted into and through the bladder outlet. Unless the outlet seems smaller than normal, in which case the vesical neck fits very snugly about the finger, we do not enlarge it. However, if the outlet is snug, a wedge-shaped triangle is removed from its posterior lip with either a punch forcep or the scissors. Minor bleeding in the edges of this wound are easily controlled with the coagulating current. It should be pointed out that in this operation the bladder neck is normally left intact after enucleation of hypertrophied lobes. It thus hangs free in the upper margin of the prostatic cavity, unsupported by any immediate peripheral attachments, and with healing of the wound contracture of the outlet may result. Because of the occurrence of postoperative bladder-neck obstruction in 5 of his first 75 cases, Millin now apparently does a wedge resection almost routinely unless the outlet has been unduly stretched or torn. In the latter event, it is a simple matter to close the outlet to the proper caliber by one or two plicating sutures of No. 00 chromic catgut.

With the prostatic cavity still exposed, a No. 20 to 24 Fr. Foley balloon catheter (30-cc. capacity) is inserted into the external meatus of the penis and is passed through the urethra into the prostatic cavity. Its tip is grasped with forceps and thereby guided into the bladder (Fig. 6). The balloon is distended with 25 to 30 cc. of sterile water or saline solution, and the catheter is then pulled down so that the distended balloon rests lightly against

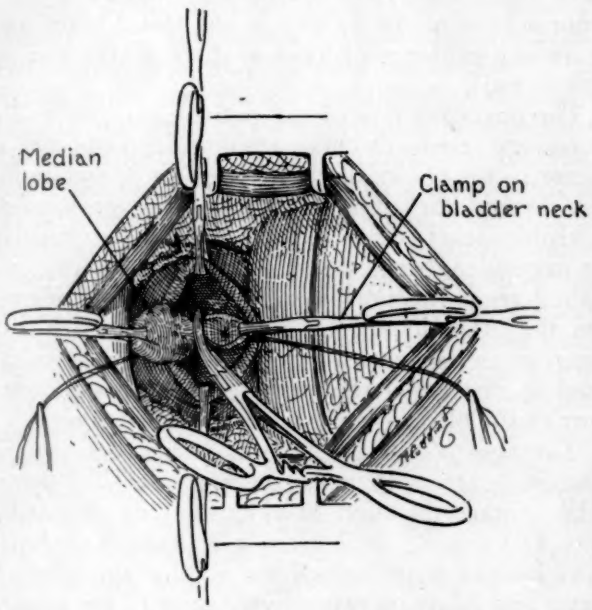

FIGURE 5. *The Lateral Lobes Have Been Removed, and the Prostatic Cavity Is Exposed.*

A small median or subtrigonal lobe has been enucleated from beneath the posterior vesical lip, and its attachment to the mucous membrane of the bladder outlet has been clamped prior to complete removal.

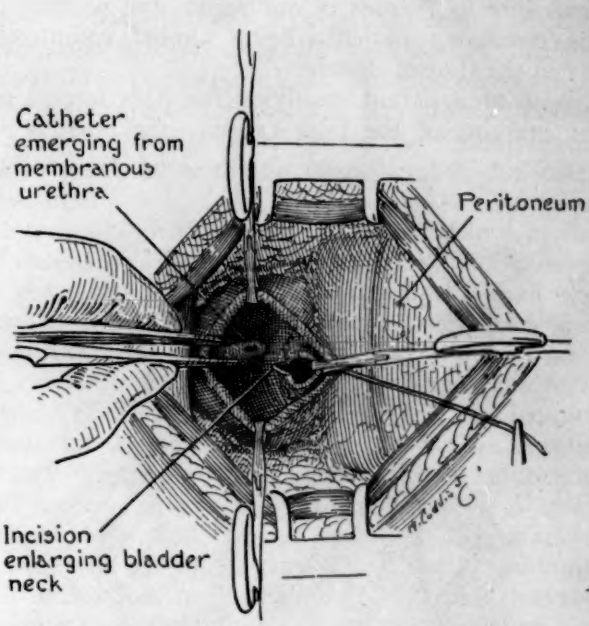

FIGURE 6. *The Prostatic Cavity and Bladder Neck Are Completely Exposed after Removal of All Obstructing Tissue.*

A wedge resection of the posterior vesical lip has been made, to enlarge the bladder outlet. A No. 20 to 24 Fr. Foley balloon catheter is being passed into the bladder preparatory to closure of the prostatic capsule.

the vesical neck. This maneuver not only assures one of the integrity of the balloon but also demonstrates any abnormal disparity between size of balloon and caliber of outlet. A final inspection of the prostatic bed is made. Should oozing be unusual and not controlled by previous ligature or fulguration, the cavity may be packed with fibrin foam or some similar hemostatic agent as described by Quinby[16] and others. We have resorted to this procedure in 7 cases of our series, the wounds in the remaining patients being almost completely dry at the time of closure.

With an assistant steadying the Allis forceps on the margins of the false capsule, the opening in this structure, now converted into a more or less transverse one by the stretching subsequent to enucleation, is closed transversely with interrupted sutures of No. 00 chromic catgut. The incision in the true capsule and endopelvic fascia is closed in a similar fashion with fine silk sutures (Fig. 7). The bladder retractor is removed, and the catheter is irrigated with sterile saline solution. If the catheter is properly adjusted and the capsular wound closed tightly, there should be no leakage when irrigation is performed. All swabs and packs are removed, and the prevesical space is irrigated with saline solution and sucked dry to remove clots. An empty Penrose drain is placed down to the suture line in the prostatic fascia and is brought out through the lower angle of the abdominal wound. The self-retaining retractor is removed, and the rectus sheath, the subcutaneous tissue and the skin are approximated with interrupted silk sutures. A dry sterile dressing is applied. Bilateral vasectomy may be performed either before or after prostatectomy. In our cases vasectomy has not been done, and we have had 2 cases of epididymitis. The catheter is again irrigated to establish its patency, at which time the returns are generally only faintly or moderately blood tinged, and is then connected to a sterile, constant-drainage system.

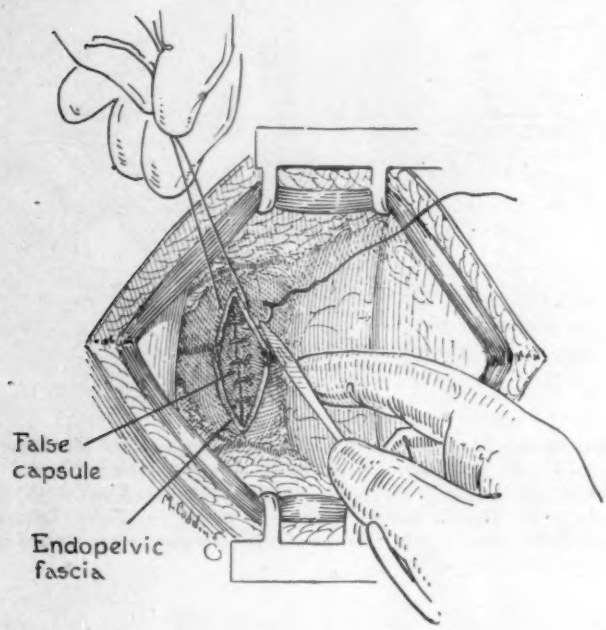

FIGURE 7. *Transverse Closure of the False Capsule and Endopelvic Fascia, Two Layers of Interrupted Sutures Being Used.*

During the fifteen-month period from June, 1946, to September, 1947, we have treated at the Peter Bent Brigham Hospital 20 cases of prostatic obstruction by the retropubic method of Millin. These cases do not represent a consecutive series. Inasmuch as the method was new and relatively untried, the selection of patients was in general limited to those with a preoperative diagnosis of benign hypertrophy of the prostate without other major complicating diseases of the lower urinary tract. One patient had coexisting bladder calculi, 4 had pathological evidence of associated chronic prostatitis, another had small prostatic calculi in a hyperplastic gland, and 2 were discovered on microscopical examination of the removed specimens to have small previously unsuspected islands of carcinoma in situ. In neither of the last 2 cases was there any evidence of local or distant extension of tumor cells.

The operative risk of the patient, relative to his renal and cardiovascular equilibrium, was not a factor in the choice of these cases for operation by this method. Seven of this group had severe arteriosclerotic heart disease with cardiac arrythmias or decompensation, while 3 had permanently impaired renal function of mild to moderate degree. On the other hand, the retropubic approach was not chosen for patients with marked intravesical median-lobe hypertrophy, pure fibrosis or contracture of the bladder neck, or prostatic carcinoma.

The ages of the 20 patients varied between 53 and 86 years, with an average age of 70.2 years. The average duration of symptoms of prostatism was 3.65 years. In 2 cases a transurethral resection had been performed for similar symptoms 6 years and 2.5 years respectively prior to the present hospital admission.

Four patients were admitted to the hospital with complete obstruction, 8 had partial retention, and 8 carried only a small amount of residual urine. There was a mild to moderately severe lower-urinary-tract infection in 12 cases, and upon admission to the hospital the blood urea nitrogen was appreciably elevated in 6. In 3 of the latter group the blood urea nitrogen dropped to normal after the institution of drainage, but the other 3 maintained a reading persistently above normal in spite of adequate drainage.

Preoperative drainage of the bladder was effected through a small urethral catheter in 12 cases, the duration of preliminary drainage varying between

6 and 25 days, with an average of 14.4 days. A No. 16 Fr. Foley catheter with a 5-cc. balloon was found to be quite effective, and the drainage was accompanied by very little evidence of local irritation.

The smallest prostate gland weighed 13.5 gm., and the largest 125 gm.; the average being 42.1 gm. The majority of glands were the site of trilobar enlargement, the median lobe being of a size equal to or smaller than the lateral lobes. In a few cases hyperplasia was confined to the lateral lobes, the median lobe being normal.

During the performance of the operation, several variations in technic were utilized. In 16 cases a transverse capsular incision was made, whereas in 4 cases a linear incision was used. Although there seemed to be less bleeding from the large prostatic veins with the linear incision digital manipulation during enucleation tends to extend this type of incision too far toward the apex of the gland and toward the vesical neck and thus to render subsequent closure of the capsule and fascia more difficult than when a transverse incision is made. Therefore, a transverse capsular incision is favored. As a result of the later development of contracture of the vesical neck in the first 3 patients upon whom we performed this operation, the bladder outlet was dilated digitally prior to closure in 12 of the remaining cases, and a wedge resection of the posterior lip was performed in 3. Plication of the outlet to reduce it to a normal caliber was performed in 2 cases in which removal of large median or subtrigonal lobes had unduly torn or stretched the vesical neck. One patient with benign hypertrophy, multiple vesical calculi and chronic cystitis underwent a combined retropubic prostatectomy and suprapubic cystotomy with removal of the calculi. Both the urethral and the suprapubic transvesical methods of drainage were used postoperatively. Except in 2 cases in which No. 20 Fr. and No. 26 Fr. catheters were used respectively, postoperative urethral drainage was maintained with either a No. 22 Fr. or a No. 24 Fr. Foley catheter with a 30-cc. balloon.

After operation the urine was clear on inspection within twenty-four hours in 9 cases, within forty-eight hours in 8 cases, and within seventy-two hours in 3 cases. The suprapubic drain was removed, in almost all cases, on the second or third day after operation. In 2 cases in which drainage was negligible the drain was removed twenty-four hours postoperatively. There was generally a moderate amount of serosanguineous ooze from the lower angle of the wound for twenty-four to forty-eight hours, but thereafter drainage was slight, and in the majority of patients the wound was dry and completely healed when the sutures were removed on the sixth or seventh day after operation. The urethral catheter was removed, on the average, slightly over six and a half days after operation, the shortest period of postoperative drainage being four days and the longest period being nine days. It was necessary to reinsert the catheter in 1 case from the ninth to the thirteenth postoperative day because of a large amount of residual urine secondary to an atonic cord bladder, in another from the tenth to the twelfth day because of bleeding and in a third from the twelfth to the sixteenth day because of suprapubic urinary leakage in a patient who had also undergone a cystotomy for removal of bladder stones. The last patient had a rather severe cystitis before and after operation and was the only one in the series to demonstrate partial incontinence, which persisted until the twenty-eighth day after operation.

Suprapubic leakage of urine occurred in 4 of the 20 cases. In 2 of these, the second and third cases of the series, there was slight drainage from the first to the fourth day postoperatively in 1 and from the sixth to the twelfth day in the other. The cause in both was attributed to faulty adjustment of the urethral catheter and inadequate closure of the prostatic capsule and fascia. A mild wound infection, manifested by local induration and tenderness, was noted in both cases. A third patient, who had vesical calculi and a marked cystitis and was subjected to a combined cystotomy and retropubic prostatectomy, had some leakage of urine from the upper angle of the wound on the tenth to twelfth days after operation. His wound was dry on the thirteenth day after urethral catheter drainage had been reinstituted from the twelfth to the sixteenth postoperative day. The fourth patient, an elderly malnourished man with severe cardiac disease, who had been bedridden for two months prior to hospitalization with chronic cystitis and prostatitis as well as prostatic obstruction, developed an infected hematoma of the prevesical space that was drained on the fifth day after operation. This was followed by suprapubic leakage of urine for a period of three weeks, after which the wound healed spontaneously. With increasing experience regarding proper adjustment of the catheter and watertight closure of the capsule we believe that urinary leakage should rarely occur except in cases in which gross infection of the prevesical space supervenes.

Other postoperative complications in this group of patients were infrequent and relatively unimportant. One patient developed transient edema of the penis on the seventh day after operation. This subsided completely in two days after the application of wet heat and elevation of the organ. Mild unilateral epididymitis occurred in 2 cases, in both of which the infection subsided rapidly with conservative measures. Acute unilateral pyelonephritis on the tenth postoperative day was noted in 1 case. Symptoms and signs abated within thirty-six hours, and the patient was discharged

from the hospital on the seventeenth day after operation with only a moderate number of pus cells in the urine. Two patients, both of whom had a marked cystitis before operation, continued to show a moderate pyuria during their period of postoperative hospitalization. However, within six to eight weeks after discharge from the hospital, the urine of both patients was free of leukocytes. It is noteworthy that in the majority of our cases the urine was unusually clear after prostatectomy by the retropubic approach.

Immediate postoperative hemorrhage occurred in 1 case, and delayed bleeding of minor degree was encountered in 2. In the first excessive bleeding into the bladder persisted for forty-eight hours after operation, and frequent irrigations were necessary to evacuate clots and maintain satisfactory drainage. Thereafter, bleeding rapidly subsided, and the urine was clear within seventy-two to eighty hours. Another patient, whose catheter was removed on the sixth day after operation, had faintly blood-tinged urine on the following day. There were no accompanying symptoms of irritation or obstruction, and bleeding ceased spontaneously within twelve to eighteen hours. A third patient, in whom the catheter was removed on the seventh day after operation, developed sudden bleeding and clot retention on the tenth postoperative day. The use of an indwelling catheter for forty-eight hours sufficed to control this complication. In none of these cases was urinary infection a contributing factor.

One other complication encountered is that related to proper maintenance of urethral-catheter drainage. In 2 cases the urethral catheter was pulled out of the bladder during the first twelve hours after operation. In both, a faulty balloon was responsible for this event, the bag apparently having burst in 1 case and having developed a slow leak in the other. Fortunately, the accident was discovered promptly before the bladder had become distended, and a new catheter on a stylet was reinserted through the urethra without difficulty. No bleeding or other untoward results followed in either case.

In the 20 cases in this series, 12 patients were discharged from the hospital within eleven to fourteen days after operation, and 6 within fourteen to twenty-one days. One patient was discharged on the thirtieth day, and one on the thirty-third postoperative day. There were no deaths. All the patients have been observed closely since discharge from the hospital, the period of follow-up observation varying between two weeks and fourteen months; 6 patients have been followed for 6 months or more, and 14 have been observed for less than six months. One patient, who had benign hypertrophy and carcinoma in situ, died of coronary thrombosis three months after operation. Immediately prior to the attack it had been noted that his only urinary symptom was mild nocturia associated with a few leukocytes in the sediment. Post-mortem examination revealed an adequate bladder outlet and no evidence of carcinoma. The remaining 19 patients are living and well. Three of these, the first 3 patients operated upon by the retropubic approach, developed a contracture of the vesical outlet within five to twelve weeks after operation; in 1, acute clot retention followed instrumental urethral investigation five and a half weeks after operation. Suprapubic cystotomy and dilatation of the contracted bladder neck were performed, with an uneventful convalescence. The patient was asymptomatic a year later. The second patient was found to have a stenosed outlet three months postoperatively. Urethral dilatation with sounds was performed on several occasions, and this patient was also asymptomatic ten months later. In the third patient symptoms of bladder irritability and infection appeared shortly after discharge from the hospital. Seven weeks after operation examination revealed a "bar" contracture of the posterior vesical lip and a rather marked cystitis. In spite of prolonged chemotherapy and local treatment in the form of dilatations and irrigation, the symptoms and signs persisted. A recent examination, conducted a year after operation, revealed the presence of a vesical calculus as well as a chronic cystitis and stenosis of the bladder neck. It is planned to perform a transurethral litholapaxy and resection of the outlet on this patient in the near future. A fourth patient, who had a chronic epididymitis preoperatively and an exacerbation of the infection postoperatively, developed a recurrent epididymitis a week after discharge from the hospital. This eventually necessitated orchidectomy several days later, approximately a month after prostatectomy. The remaining 15 patients have had no urologic complaints referable to the operation since discharge from the hospital.

Summary

The pertinent literature concerning a newly proposed method of retropubic prostatectomy is briefly reviewed, and the advantages and disadvantages of the procedure are discussed.

The indications and contraindications for the employment of this operative approach are presented in the light of a limited experience with the operation.

The technic of the operation is outlined, and a summary of the results obtained in a selected group of 20 cases is recorded.

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AMEBIC ABSCESS OF THE LIVER*

Therapeutic Problems in Various Types of Late Hepatic Amebiasis

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THE problem of late complications of disease acquired by military personnel in distant parts of the earth is now facing the medical profession throughout the United States. In all probability it will continue to do so for some years to come. In the six-month period from November 1, 1946, to May 1, 1947, at the Veterans Administration Hospital, West Roxbury, Massachusetts, 6 patients were treated for amebic liver disease secondary to amebiasis acquired while on overseas duty one or two years before. It seems likely that, with the long delay that may take place between the initial infection and the late complication, new cases will continue to appear in areas of the country where the disease is customarily considered as being relatively uncommon. We present these 6 cases, discussing the signs and symptoms, the forms of treatment used, and suggest a plan of treatment that utilizes all aids now currently available.

It has long been known that the high mortality that follows open drainage of an amebic abscess is due to secondary infection entering through the draining site. In 1871 MacLean[1] pointed out that the death rate was lowest in liver abscesses that discharged through the lungs and highest in those draining through the abdominal wall. He advocated the removal of the pus by means of a Bowditch syringe without the admission of air. This method of treatment was abandoned because there was usually a reaccumulation of the material in the abscess cavity, probably owing to the lack of suitable antiamebic chemotherapy. The discovery of the specific effect of injections of emetine by Rogers[2] in 1912 led to a readoption of the closed aspiration method of treatment in conjunction with the use of emetine to prevent reformation of the abscess. Ochsner and DeBakey[3] reported that in patients treated by open drainage without amebacides the mortality was 48.2 per cent. On open drainage in addition to emetine, the mortality was 16.6 per cent. Of those treated on emetine alone, only 5.4 per cent died. They also stated that in cases in which drainage through a bronchus had already been established, antiamebic treatment was sufficient. Walters et al.[4] recommend that open drainage be reserved for cases in which the abscess cavity obviously has become secondarily infected, or in which rupture into either the pleural or the peritoneal cavity is impending. The latest edition of *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*[5] recommends open drainage in a well established abscess. Berne[6] concluded that closed aspiration and emetine treatment reduced the mortality to its lowest level. In the early stages of amebiasis of the liver, Klatskin[7] has clearly shown that repeated courses of emetine alone were sufficient to effect cure.

MATERIALS AND METHODS

For discussion of therapy our clinical material is divided into three groups: simple amebic hepatitis, possibly with small abscess formation; a large liver abscess that remained localized within the abdomen; and a large abscess that penetrated through the diaphragm.

Only 1 patient (Case 1) was classified as having diffuse hepatitis without significant abscess formation. He was treated with chemotherapy alone, surgical measures being unnecessary.

Two patients (Cases 2 and 3) had abscesses of significant size that had not drained spontaneously into either the pleural or peritoneal cavities. Both exhibited tender, palpable masses beneath the right costal margin. They were treated by chemotherapy and aspiration. After the institution of emetine therapy, an incision was made in the abdominal

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wall to permit, under direct vision, the introduction into the abscess of a large aspirating needle on a syringe. Aspiration was followed by the instillation of penicillin into the abscess cavity and closure of the abdominal wall without drainage. At least one additional course of emetine was administered before discharge from the hospital.

Two of the abscesses that had penetrated through the diaphragm (Cases 4 and 5) were considered to be secondarily infected. These were treated with open drainage.

In another case (Case 6) the abscess had drained spontaneously into the right pleural cavity and through the bronchial tree. The patient was treated with chemotherapy and aspiration of the empyema fluid by thoracentesis.

All patients were treated with intramuscular emetine in a single daily dose of 60 mg. (1 gr.). The initial course lasted for at least eight days, and subsequent courses were of six days' duration. At least two courses were given to each of the patients. The pulse and blood pressures were recorded three times a day, and electrocardiograms were taken before and on every second day of treatment to determine the existence of drug toxicity. After each course of emetine, all patients received vioform (iodochlorohydroxyquinoline) in oral dosage beginning at 0.25 gm. (4 gr.) three times daily, and slowly increasing to 1.0 gm. (15 gr.) three times a day. Dosage at this level was maintained for seven to ten days. Penicillin was injected intramuscularly in doses of 30,000 to 50,000 units every three hours, concurrent with or prior to the initiation of the first course of emetine. It was continued as long as fever or signs of secondary infection were present. The arsenical amebacides were not used.

Case Reports

Case 1. L. K., a 25-year-old man, was admitted to the hospital on October 1, 1946, complaining of chills, fever and right-upper-quadrant pain of 7 days' duration. In June, 1945, while serving in the Philippines, he had experienced an intermittent episode of watery diarrhea of 3 weeks' duration, which had subsided spontaneously. Chills and fever due to a malarial infection had been experienced in December, 1945, and April, 1946. One week before admission, while riding in a truck, he had noted sharp, knife-like periumbilical pain, which had later shifted to the right upper quadrant. The pain was aggravated by deep breathing and pressure.

Physical examination revealed the patient to be acutely ill. A tender liver was palpable on inspiration.

The temperature was 102°F., the pulse 100, and the respirations 20.

Examinations of the blood showed white-cell counts of 12,000 to 18,000, with a marked increase in neutrophils. The sedimentation rate was 20 mm. per hour. Blood cultures were sterile. Urinalysis was negative. Except for an elevated urobilinogen, routine liver-function tests were within normal limits. After several unsuccessful attempts, typical cysts of *Endamoeba histolytica* were found in the stool. X-ray examination of the chest and fluoroscopy were not remarkable.

The patient ran a daily spiking temperature from 99 to 103°F. On the 4th hospital day penicillin therapy, consisting of 30,000 units intramuscularly every 3 hours, was begun. The temperature was lower on the 7th to 9th days, but the symptoms remained unchanged. On the 9th hospital day, emetine therapy was instituted, with slow improvement, the temperature falling to near normal by the 3rd day of this treatment. Emetine and penicillin were continued for a total of 10 days without evidence of drug toxicity and were followed by a course of vioform for a similar period. On October 31 and November 2 a high spiking temperature recurred. Thick blood smears revealed *Plasmodium vivax*, and the fever promptly responded to therapy with chloroquin. A second course of emetine was instituted for 6 days after completion of the antimalarial therapy. The patient was discharged November 20, with the diagnoses of amebic hepatitis and malarial fever. During the succeeding month he experienced occasional fever and a constant dull ache in the right upper quadrant. Readmission on December 27, for a third course of emetine and a second course of chloroquin, was followed by the disappearance of all symptoms. When last seen in September, 1947, he was working and in good health.

Case 2. W. M., a 24-year-old laborer, was first admitted to the hospital on November 30, 1946, complaining of right-upper-quadrant pain of 2 days' duration. He had had mild abdominal cramps and watery stools on several occasions while on duty with the United States Army in New Guinea and the Philippines in 1944–1945. He had been evacuated to the United States in 1945 because of skin lesions of the legs and feet. Symptoms had first appeared 2 days before admission, when he had suddenly developed a pressing pain in the right upper quadrant radiating across the back. A temperature of 102°F. developed, and he was treated at home with sulfadiazine before being admitted to the hospital. His appetite had remained unaffected.

Physical examination showed moderate tenderness and spasms over a mass in the right upper quadrant.

The temperature was 101°F., the pulse 100, and the respirations 25.

The white-cell count was 18,000, with 63 per cent neutrophils. A chest film was normal. It was believed that the diagnosis lay between an acute cholecystitis and an amebic abscess presenting beneath the right costal margin. A preliminary dose of emetine was given, and an exploratory laparotomy performed. The liver was found to be enlarged, the edge extending to the level of the umbilicus. An aspirating needle removed 70 cc. of thick, reddish, purulent material typical of an amebic liver abscess from the right lobe. Penicillin, 50,000 units in 10 cc. of saline solution, was injected into the abscess cavity, and the abdomen was closed without drainage. Smears of the aspirated fluid were negative for amebas, and a culture grew out *Proteus vulgaris*. Postoperatively, penicillin was continued intramuscularly for 19 days. The course of emetine was discontinued after six doses because of changes in the electrocardiogram. The temperature fell to normal on the 4th postoperative day and remained at that level. On December 13 a course of vioform was initiated. On January 6 a second course of emetine was begun, being discontinued after 6 days because of recurrence of the electrocardiographic changes. This was followed by two further courses of vioform and another course of emetine. At no time were amebas found in the stools. The patient was discharged, asymptomatic, on February 4, 1947. He has remained well.

Case 3. W. K., a 25-year-old musician was admitted to the hospital on February 26, 1947 complaining of sudden onset of fever and a severe, sharp, catching pain across his upper abdomen, increased by cough or pressure. In July, 1945, while serving in the Philippine Islands, he had experienced a severe episode of diarrhea of 10 days' duration, followed by 6 weeks' hospitalization for jaundice and malaria. Loose stools, two or three times a day, and monthly malarial attacks had been noted since 1945.

Physical examination revealed a temperature of 100°F., and a hard, markedly tender liver edge three fingerbreadths below the right costal margin near the midline. There was a moderate polymorphonuclear leukocytosis, and the stools contained numerous actively motile trophozoites of *E. histolytica*. A course of emetine was begun on February 28 and penicillin on March 3. On the following day under nitrous oxide, oxygen and ether anesthesia, a 2.5-cm. incision was made over the point of greatest tenderness beneath the right costal margin. An abscess that had become

adherent to the anterior abdominal wall was entered. Over 30 cc. of thick, pinkish-red, purulent material evacuated itself through the incision, and, after irrigation, 200,000 units of penicillin was instilled before the incision was closed. No amebas were found in the pus. The temperature was normal thereafter, and all symptoms rapidly disappeared. Emetine was discontinued after 9 days because of electrocardiographic changes, which proved to be of a temporary nature. A course of vioform was followed immediately by 6 more days of emetine. Changes in the T waves recurred, but on complete bed rest, these were greatly lessened. The patient was discharged on April 2. Follow-up examinations have been negative.

CASE 4. J. Z., a 19-year-old veteran, was first admitted to the hospital on August 16, 1946, complaining of right-upper-quadrant pain, chills and fever of 4 days' duration. In 1945 he had had a cystotomy for removal of paraffin, which had been introduced into the bladder through the urethra. From early 1945 to June, 1946, he had been on active duty in Guam and China, but there was no history of dysentery while he was in the service. About 1 week prior to admission he suffered an attack of diarrhea lasting 1 week. Four days before admission he complained of chills and a feeling of oppression in the right anterior portion of the chest and the right upper quadrant. The temperature was 103°F. on admission. A tender liver was palpated three fingerbreadths below the right costal margin. Urinalysis revealed a ++ test for albumin and 50 to 60 pus cells per high-power field. The white-cell count was 12,850, with 81 per cent neutrophils. Examination of the stools was negative. Because of acute pain in the right lower quadrant with tenderness and spasm, an exploratory laparotomy was performed on the day after admission. An attempt at liver aspiration yielded no pus, and a fibrotic retrocecal appendix was removed. Postoperatively, on penicillin therapy alone, the high temperature subsided to normal within 7 days. The patient was discharged on the nineteenth postoperative day entirely asymptomatic.

Five days later he returned, complaining of a chill, which had appeared 2 days prior to readmission, a feeling of discomfort in the right side of the abdomen and a pain in the right shoulder and neck. Physical examination showed some tenderness in the right upper quadrant, with slight voluntary spasm. The temperature was 103°F. A moderate polymorphonuclear leukocytosis was present. The urine was normal. Examination of the stool was again negative for amebas, and a proctoscopic examination was negative. Both penicillin and sulfadiazine therapy were begun. On the 17th day the sulfadiazine was stopped because of lack of improvement, and a course of emetine was given. The temperature and white-cell count promptly fell to normal. The emetine was followed by a course of vioform. A retrograde pyelogram was done on September 15 because of urinary symptoms, which revealed a right hydroureter and blunting of the pelvic calyxes on the right. A culture of the urine from the right kidney grew colon bacilli. After the temperature had been normal for 2 weeks, the patient was discharged to be continued as an outpatient on sulfadiazine.

Two weeks later he was readmitted, having developed a fever 2 days previously, and having coughed up what he thought to be blood. On admission the temperature was 103°F., and the pulse 120. Dullness and absent breath sounds were present in the right axilla and over the right lower portion of the chest anteriorly. The abdomen showed marked tenderness and spasm in the right upper quadrant. The white-cell count was 5400, with 68 per cent neutrophils. Fluoroscopy showed elevation of the anterior mid-portion of the right leaf of the diaphragm, haziness of the diaphragmatic angle and an immobile diaphragm. Penicillin therapy was begun. On the 2nd day he coughed up a considerable amount of thick, reddish sputum in which small trophozoites resembling *E. histolytica* were found. A course of emetine was started immediately. The patient remained acutely ill. On the 6th hospital day an open drainage of a right subdiaphragmatic abscess was performed below the right costal margin. Cultures of the pus obtained were sterile.

Postoperatively the temperature continued to spike. Cultures obtained at subsequent packing of the abscess showed *Staphylococcus albus*. On the 21st postoperative day, a second operation was performed, a segment of the seventh rib in the right anterior axillary line being resected. The temperature at first fell to normal, but again became elevated, leading to the recognition of a supradiaphragmatic abscess pocket, which was drained through the lateral incision on December 23. This left the patient with a small bronchial fistula. The temperature fell to normal, and 18 days later penicillin was stopped.

Twelve days later, profuse purulent drainage, with many motile amebas, again appeared. In addition, a positive culture of *Staph. albus* was obtained. Penicillin was resumed, the drainage wound enlarged, and another course of emetine given. The temperature again fell to normal, and the drainage decreased. A second course of vioform was administered. Gain in weight and improvement in general health continued. The external drainage wound required subsequent revision 2 months later. The patient was discharged on June 27, 1947, after 7 months' hospitalization, with a bronchial fistula, but drainage sites otherwise healed. Subsequent follow-up examination showed closure of the fistula and no further symptoms.

CASE 5. T. C., a 34-year-old woolen worker, had been hospitalized with the diagnosis of bacillary dysentery in the Philippine Islands in June, 1945. Hospitalization for right-sided abdominal pain and a high temperature was initiated at this hospital in November, 1945, when tenderness and rigidity in the right upper quadrant were noted. A downhill course, with the appearance of signs over the lower lobe of the right lung, was halted by a single combined course of emetine and penicillin, after which the patient was discharged on January 7, 1946.

He was readmitted late in February for recurrence of the abdominal pain. The findings over the right lower lobe and upper part of the abdomen were again present. The white-cell count was 26,000, and for the first time, typical cysts of *E. histolytica* were found in the stool. Two alternate 8-day courses of emetine and vioform without penicillin were given during the next month without permanent effect. On March 27 under local anesthesia, a trocar was inserted through an incision over the eleventh intercostal space, and 2000 cc. of thick, reddish-brown material aspirated. Subsequently the high temperature persisted, the cavity became filled with air, and open drainage was performed on the basis that secondary infection was probably present.

Emetine and penicillin were again administered, with temporary improvement, but the high temperature and profuse drainage promptly reappeared when the therapy was discontinued. In spite of various revisions of the incision, the patient failed markedly, and the wound drained profusely during the next ten weeks, the exudate literally teeming with motile trophozoites of *E. histolytica*. Repeated intramuscular courses of emetine and emetine irrigations did not affect the number of these parasites. Resistance studies of the amebas were performed by Dr. Quentin Geiman, of the Department of Comparative Pathology, Harvard Medical School. Amebas cultured from this patient grew in concentrations of emetine that were much higher than the control strains tested, indicating resistance to the drug in vitro.

On June 25 a thoracotomy with resection of part of the eighth rib was performed, and a pleural empyema cavity with a bronchopleural fistula effectively drained. Disappearance of the trophozoites from the exudate, loss of fever and other improvement occurred from this point on. Convalescence was slow, but the wounds had healed sufficiently for discharge on December 9. Follow-up examinations have shown complete healing of all incisions. During the year of hospitalization the patient received a total dose of 3 gm. (45 gr.) of emetine intramuscularly without any evidence of toxicity.

CASE 6. J. W., a 22-year-old printer, was first admitted to the hospital on December 18, 1946, complaining of fever, cough productive of bloody sputum and pain in the right side of the chest of 2 weeks' duration.

While on overseas duty in Iran during 1944 and 1945, he had suffered two brief bouts of diarrhea not requiring hospitalization. In the month prior to admission to this hospital, 1 year after returning from overseas, he had been hospitalized elsewhere on three occasions for fever of unknown origin. He had been treated with penicillin and

sulfadiazine, and had received 1 unit of plasma. One week before admission he entered a second hospital with pain in the right side of the chest, a productive cough and fever. A needle aspiration of the right side of the chest revealed fluid typical of an amebic abscess, and he was transferred to this hospital.

The temperature was 101°F., and the pulse 96. There were signs of fluid at the right base, and a tender liver edge was palpable three fingerbreadths below the right costal margin. The white-cell count was 8750, with 56 per cent neutrophils. The stools were negative for amebas, but a sputum examination was positive for trophozoites resembling *E. histolytica*. X-ray study of the chest showed obliteration of the lower two thirds of the right lung field. Aspiration from the right side of the chest yielded 260 cc. of sterile bloody fluid containing no identifiable amebas.

Intramuscular penicillin therapy was begun, and a course of intramuscular emetine given. Two subsequent chest aspirations yielded a further 500 cc. of fluid. The liver returned to its normal position. On the 12th hospital day the temperature had fallen to normal, where it remained. Penicillin was continued for 26 days, followed by a course of vioform. This was followed by a second course of emetine, which was discontinued after 6 days because of electrocardiographic changes and the development of jaundice. Laboratory studies at that time showed an icteric index of 19, cephalin flocculation of ++++, a van den Bergh reaction of 2.1 mg. per 100 cc., later rising to 5.8 mg. (4.2 mg. direct, 1.6 mg. indirect). This was interpreted as a homologous serum jaundice caused by the plasma received during the previous hospitalization. Over the succeeding month the jaundice cleared, the liver-function tests improved, and the electrocardiogram quickly returned to normal. The patient was discharged, asymptomatic, on March 22, 1947. He was readmitted on April 21, when an x-ray film of the chest, an electrocardiogram, liver-function studies and blood counts were all within normal range. He was discharged without further therapy. Follow-up examinations have been negative.

Discussion

Patients suffering from diffuse hepatic involvement or from multiple small liver abscesses (as in Case 1) appear to respond well to adequate doses of chemotherapy alone.[7] If an accurate diagnosis can be made and proper treatment instituted, it seems likely that the complications due to penetration of the abscess into the surrounding tissues can be avoided. Single courses of chemotherapy in late larger abscesses proved inadequate. In Cases 4 and 5, if proper diagnoses had been made and adequate treatment instituted at the time of the first admission, it seems probable that many of the subsequent complications would have been prevented.

Needle aspiration of moderate-sized, individual abscess cavities readily localized by physical or x-ray examination, in conjunction with adequate chemotherapy, gave good results in Cases 2 and 3. The period of hospitalization was short, with a relatively benign postoperative course. There was suggestive clinical evidence that penicillin somehow appreciably supplemented the amebicidal action of emetine. No studies in vitro were performed to confirm this impression.

Abscesses draining spontaneously into the bronchial tree may heal on chemotherapy alone, as in Case 6. The presence of a bronchial fistula does not, in itself, necessarily mean that sufficient secondary infection has taken place to require open drainage. In the light of subsequent experience we should now treat Case 4 for a longer period with chemotherapy before resorting to open drainage. Similarly, earlier aspiration in Case 5 might have been successful. Patients who had open drainage (Cases 4 and 5) suffered a stormy postoperative course, with a prolonged convalescence. This is, in contrast with the results obtained in Case 6 by aspiration and chemotherapy without surgical drainage. Open drainage is indicated only when a thorough trial with chemotherapy and aspiration has proved inadequate. When performed, open drainage must be wide and complete, or repeated drainage procedures will be necessary. In the presence of open drainage and secondary infection, penicillin appears to be beneficial in decreasing systemic reaction and in lessening the quantity of purulent discharge, which is in itself a culture medium for amebas.

All cases should be observed for evidence of emetine toxicity. The electrocardiographic changes were the only ones noted in our series, being present in 3 of the 6 cases. Changes in contour and direction of the T waves in the limb and chest leads were noted in varying degree. They persisted for a few weeks only, were greatly lessened by absolute bed rest and were not associated with tachycardia, arrhythmia, changes in blood pressure or symptoms referable to the heart. The occurrence of such changes in the initial course was not regarded as a contraindication to further courses of emetine. Treatment continued after the development of these changes was not followed by serious effects. This varies considerably with the experience of Dack and Moloshok.[8]

The development of resistance of the parasite to emetine may take place. This was demonstrated by the studies in vitro and the clinical observations in Case 5.

Vioform was found to be an extremely satisfactory means of eradicating the cyst forms. By a gradual increase of the dose to 1.0 gm. three times daily, a highly effective intestinal concentration of the drug was attained without producing irritant or toxic symptoms. No parasites were found in stool examinations made during the follow-up studies.

It appears that the primary infection in these cases was acquired while the patients were on overseas duty, 4 having served in the Philippines, 1 in China, and 1 in Iran. Not all had had previous symptoms of intestinal disease, and in none had a diagnosis of amebic dysentery been made. The lapse of time between departure from the overseas duty and the admission to the hospital for hepatic disease varied from two to eighteen months; it can, of course, be much longer.

The onset of symptoms referable to the abscess was often acute and without premonitory symptoms. In 2 cases the physical signs suggested an

acute cholecystitis. In others the signs of perihepatitis were outstanding. Restriction of the movement of the adjacent diaphragm without deformity of shape on x-ray examination was often an early sign, and was frequently followed by subsequent pleural involvement.

Laboratory studies in similar types of cases showed the white-cell count to vary from normal to marked elevation. Examination of the stools was positive for amebas in 3 cases, or 50 per cent. Characteristic sputums, after spontaneous drainage of the abscess by hepatobronchial fistula, contained trophozoites in the 2 cases of that group. The exudate from abscess cavities that received inadequate open drainage contained large numbers of motile trophozoites.

Summary

Six cases of late amebiasis of the liver are described. None of these patients had previously been diagnosed as having amebiasis. The time of onset of symptoms after returning to the United States from overseas was variable. The onset was usually acute, with signs referable to the liver.

Three problems in therapy are described. These include diffuse hepatitis or small abscesses that heal on chemotherapy alone; large abscesses that require aspiration in addition to chemotherapy — this is most safely performed as a surgical procedure; and large abscesses penetrating above the diaphragm, which may drain spontaneously and be cured by chemotherapy with or without thoracentesis. Occasionally, open drainage may become necessary, but this should be reserved as a last resort, for it is likely to be followed by prolonged hospitalization.

The best results of chemotherapy were obtained by a combination of emetine and penicillin in two or more courses, alternately with vioform in large doses. Toxic effects of emetine on the heart as revealed by electrocardiogram were noted in 3 cases, but were apparently not serious.

All six patients are alive and well at present, but only a more prolonged follow-up will determine whether or not they have been permanently cured of the disease. The early follow-up study appears to be just as satisfactory in patients treated conservatively as in those treated by radical surgery. The former had a more benign clinical course and a shorter hospital stay than those on whom open drainage was performed.

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DESIRABILITY OF THE ROUTINE USE OF TETANUS TOXOID

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DURING the last few years a considerable amount of additional information regarding the effectiveness and hazards of active immunization against tetanus has become available. The war, with its many casualties among unimmunized, partly immunized and fully immunized civilian and military personnel, contributed greatly to this fund of information. In the light of this added knowledge and in view of the continuing diversity of opinion and practice regarding the routine active immunization of children and adults, it was believed that the entire problem deserved reevaluation. An effort was made to analyze objectively all the factors involved and to arrive at a definite conclusion whether active immunization as a public-health procedure should be limited to special groups or be administered routinely to all children or adults, or both.

METHOD

The various factors pro and con are enumerated below and analyzed on the basis of a review of the pertinent available literature supplemented by the following procedures:

A series of 100 consecutive cases of tetanus was culled from the records of five Massachusetts hospitals† and analyzed from the standpoint of the type of injury preceding the disease, the use of prophylactic tetanus antitoxin at the time of the injury and whether recovery occurred. I bear the responsibility for any errors in the presentation and interpretation of these figures.

Pools of two sample population groups were carried out to determine the prevalence of penetrating injuries and the frequency of prophylactic use of tetanus antitoxin.

Personal correspondence with all the private and public laboratories licensed to distribute tetanus antitoxin was carried on to estimate the amount used annually in the United States.

The accident-room records of 250 successive cases of injury in a representative, reputable urban hospital were examined to determine the frequency with which tetanus antitoxin is given and the type of injuries in which it is currently considered indicated.

FACTORS FAVORING ROUTINE IMMUNIZATION

The factors favoring routine immunization are as follows: the high case mortality in tetanus; the frequency of administration of tetanus antitoxin when active immunization is limited; the marked frequency of accidental injuries that may be precursors of tetanus; the wide distribution of tetanus spores and evidence that they are not limited to soil in rural areas; the allergic reactions to tetanus antitoxin; and the not infrequent failure of tetanus antitoxin prophylactically and the almost universal effectiveness of toxoid.

High Case Mortality

In spite of the advent of tetanus antitoxin, sulfonamides and antibiotics, a definitely effective therapeutic agent remains to be found.

In the last twenty to thirty years there has been little, if any, change in the over-all case mortality. The best rate in any statistically significant series is about 35 per cent, and the average is 44.7 per cent (Table 1).

Frequency of Administration of Tetanus Antitoxin

To keep the incidence of tetanus low when active immunization is limited, it is necessary to give many doses of tetanus antitoxin. It is obvious that if a sufficiently large number of doses were given, the undesirable effects of this mass sensitization might well overbalance the advantage of omitting routine inoculations of tetanus toxoid.

Two separate methods were used to estimate the frequency of administration of tetanus antitoxin. The first was correspondence with all private and public laboratories licensed to distribute tetanus antitoxin through the Biologics Control Laboratory of the United States Public Health Service. Replies were received from nine out of ten of the private concerns, and annual reports supplemented by correspondence elicited similar figures from all the health departments concerned. From these figures an estimate of the total distributed annually could be made. This would not include tetanus antitoxin packaged for therapeutic use. Undoubtedly, some of this is used prophylactically. It would also exclude any private laboratories whose products were not sold in interstate commerce.

As the replies from many of the private companies were confidential, an individual breakdown could not be given. However, the over-all figures of public and private laboratories amounted to approximately 2,125,000 doses of 1500 units annually, exclusive of returns when the expiration date was exceeded.

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†The institutions concerned are the Massachusetts General, Beverly, Beth Israel, Boston City and Peter Bent Brigham hospitals. The courtesy and assistance of the administrative staff and record-room workers are gratefully acknowledged.

The second method may be considered complementary to the first. It consisted of polls inquiring of two types of population groups whether they remembered ever having received tetanus antitoxin. One type consisted of young adults of moderately high economic level, the majority of whom could be said to have medical attention more readily available than the average person. These were the current group of Harvard medical students.* The information was obtained by checking the routine medical-history forms filled out on admission to the school. The other type of population group was the total adult medical and surgical ward patients of two Massachusetts hospitals. Information was obtained by personal questioning of each patient. In addition to the query about prior tetanus antitoxin, the patients were also asked whether they had ever received a severe burn or a penetrating wound (the example of stepping on a nail was used) *without* the administration of tetanus antitoxin.

TABLE 1. *Case Mortality in Various Series.*

AUTHOR	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Gruich[1]	289	137	47.4
Vinnard[2]	352	158	44.9
Huntington[3]	642	405	63.1
Bruce[4]	1,437	500	34.8
Gessler[5]	121	65	53.7
Press	100	49	49.0
Totals	2,941	1,314	44.7

Similar information on the prevalence of prior inoculation of horse serum (not limited in this series to tetanus antitoxin) was gathered from an article by Lyall and Murdick.[6] In 1000 consecutive cases of accident in which tetanus antitoxin was given, a history of whether or not prior horse serum had been received was obtained from 815 patients. Of these, 110 (13.5 per cent) had had serum before. This percentage is similar to that noted in the ward cases. Both series are definitely significant from the statistical standpoint.

It is thus noted that from 11 to 27 per cent of the general population remember having had antiserum inoculations. In addition, a large number may have received it during the first five or six years of life, when it would rarely be remembered. It is during that time that accidental injuries associated with falling and creeping and often necessitating tetanus antitoxin are especially frequent.

A factor further highlighting the allergic potentialities is brought out in the above series of Lyall and Murdick[6]: many persons receive more than one dose of antitoxin during their lifetime. For example, the 110 persons mentioned above with a history of prior administration of horse serum were not denied a dose of tetanus antitoxin because of this history. They constitute a portion of the growing group of persons that have had two or more doses of foreign proteins parenterally. Each succeeding dose greatly increases the risk of severe reactions and anaphylaxis. In the series of 1000 cases referred to,[6] generalized reactions occurred in 23.6 per cent of those giving a history of prior serum injection and in only 8.8 per cent of those without such a history.

*Permission to examine these records was obtained through the courtesy of Dr. Myles P. Baker.

TABLE 2. *Prior Injections of Antiserum among Medical Students.**

DATA ON INJECTIONS	NO. OF STUDENTS
History of 1 or more	109 (27.3%)
None admitted	242
No reply	49
Total	400

*The subjects questioned were second-year, third-year and fourth-year students at Harvard Medical School.

Frequency of Injuries that May Result in Tetanus

To estimate the frequency of these injuries it is necessary to arrive at a definite understanding of the types concerned. It has been rather generally believed until recently that penetrating wounds and embedded foreign bodies, especially if contaminated with rural soil, as well as severe burns, accounted for the large majority of cases of tetanus. These wounds, in addition to gunshot wounds and those in which there was considerable maceration and destruction of tissue, were the ones for which tetanus antitoxin was recommended.

TABLE 3. *Prior Injections of Antiserum among All Surgical and Medical Ward Patients in Two Massachusetts Hospitals, according to a Personal Poll.*

DATA ON INJECTIONS	NO. OF PATIENTS
Prior tetanus antitoxin	17 (11.0%)
No tetanus antitoxin but history of penetrating injury or severe burn in past	29 (18.8%)
Total	154

An approximate gauge of the frequency with which this type of wound is remembered can be obtained from Tables 2 and 3, if one assumes that the persons who received tenanus antitoxin did so because of the above type of wound. This is a reasonable assumption, and in the 154 patients personally polled (Table 3) it was corroborated. It is thus noted that approximately 30 per cent of the population can recall such an injury. Again, it is to be expected that many persons had such in-

juries at too early an age to recall them. Indeed, if splinters are included in penetrating injuries, it is reasonable to believe that the majority of the people have had such episodes.

Recently, evidence has become more prevalent that tetanus very frequently is preceded by non-penetrating wounds and that often a trivial injury results in the disease. Moreover, in a moderately large proportion of the cases, no history of any injury can be obtained. This implies that any wound sustained was so slight that it went unnoted. This concept is not really a new one and has been recognized by a few physicians for many years. In 1923 Miller[7] stated that it was to be noted that tetanus could come from wounds so slight and so superficial that they were hardly noticeable, and that it was not at all unheard of to have a clear-cut clinical case and yet be unable to find the focus of the disease. Many studies of tetanus reported in the literature reveal no injury or very slight injuries (too slight to implicate a physician) and several of these series are listed in Table 4. Pratt,[8] in 1945, was the first to place strong, definite emphasis on this point.

TABLE 4. *Frequency of Trivial Injuries and "Unknown Injuries" Preceding Tetanus.*

AUTHOR	TOTAL CASES OF TETANUS	INJURY UNKNOWN		INJURY TRIVIAL	
		NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Vinnard[3]	352	38	10.8	*	*
Pratt[8]	56	16	28.6	18	32.1
Dean[9]	25	*	*	5	20.0
Francisco[10]	100	16	16.0	28	28.0
Silverthorne[11]	70	15	21.4	37	52.9
Spaeth[12]	276	37	13.4	*	*
Dietrich[13]	28	13	46.4	*	*
Press	100	14	14.0	33	33.0
Totals for unknown injuries	982	149	15.2		
Totals for trivial injuries	351			121	34.5

*Information not stated.

Of the 100 consecutive patients with tetanus admitted to the five metropolitan Massachusetts hospitals, 33 had injuries of a nonpenetrating type that were so trivial that medical attention would not have been sought even by the patients in the highest income levels. Examples of this type of injury are infected mosquito or chigger bites, superficial cuts or scratches on the palms, soles, wrist or the dorsum of the hands and slight abrasions of the knee or elbow. In addition, 14 patients in spite of careful questioning could recall no injury whatsoever in the five or six months preceding the onset of the illness.

It is unquestionably true that the vast majority of trivial injuries are not followed by tetanus, and even most of the penetrating wounds might not result in tetanus if unprotected. However, in view of the fact that about 50 per cent of the cases of tetanus are preceded by very slight wounds or "no" wounds and the case mortality is about 45 per cent, the conscientious physician would find it difficult to avoid administering tetanus antitoxin in such cases. The problems inherent in such frequent use of tetanus antitoxin are obvious and constitute an excellent point favoring routine use of tetanus toxoid.

Wide Distribution of Tetanus Spores

In the majority of cases, medical teaching has transmitted from one textbook to the next the concept that tetanus spores are generally associated with horses and other grazing animals. More recent investigations using refined anerobic technics combined with animal inoculation fail to give uniformly conclusive results. The technic involved is a rather intricate one, and this probably accounts for the difficulty in isolation of the spores from feces and the diversity of the results obtained. For example, Tulloch,[14] in a very detailed and thorough

TABLE 5. *Distribution of Tetanus Spores.*

AUTHOR	DATE	LOCATION	SPECIMENS EXAMINED		POSITIVE	SPECIMENS
			NO.	TYPE	NO.	PERCENTAGE
Pizzini[15]	1898	Italy	100	Human feces	5	5.0
Tulloch[14]*	1919	England	52	Human feces	12	23.1
Tenbroeck and Bauer[16]	1922	China	78	Human feces	28	35.9
Tenbroeck and Bauer[17]	1926	China	539	Human feces	153	28.4
Fildes[18]†	1925	England	200	Human feces	2	1.0
	1925	England	200	Horse feces	34	17.0
	1925	England	70	Soil	33	27.1
Buzello and Rahmel[19]	1924	Germany	50	Human feces	20	40.0
Bauer & Meyer[20]	1926	California	487	Human feces	120	24.6
Kerrin[21]‡	1928	England	204	Human feces	0	0
Kerrin[22]	1929	England	53	Horse feces	5	9.4
	1929	England	37	Dog feces	9	24.3
	1929	England	141	Rat feces	23	16.3
	1929	England	100	Human feces	0	0
Kahn[23]	1924	New York City	72	Human feces	0	0
Gilles[24]	1937	Baltimore	63	Street dust	9	14.3

*Seven positive specimens were found in 21 soldiers returned from the European Theater
†No separate test was reported to distinguish toxic from nontoxic strains.
‡Controlled by one specimen from human tissue and not by known positive feces

study, was able to isolate tetanus bacilli from only about half the cultures obtained from *wounds* (not feces) of 200 patients with clinical tetanus. In the light of this, it is easier to understand the discrepancy in reported investigations. In addition, varying geographic, occupational and sanitation features may be involved.

Table 5 presents a summary of most of the reported studies on this subject.

In the presence of conflicting evidence and a difficult technical procedure, it is reasonable to place more weight on the isolation of tetanus bacilli than on the failure to isolate them. This conclusion is strengthened by the commonly accepted empiric observation that severe burns and wounds with considerable necrosis are likely to result in tetanus if no prophylactic antitoxin is given, regardless of the absence of contamination with rural soil. Study of Table 5 reveals the rather startling fact that tetanus spores are frequently found more often in the feces of human beings than in those of horses.

Allergic Reactions to Tetanus Antitoxin

In addition to local reactions at the site of injection, generalized allergic reactions, palsies of the peripheral and central nerves and deaths due to anaphylactic shock have repeatedly been described. The incidence of these reactions varies with the purity of the antitoxin, the method of administration, the use of concomitant epinephrine, the criteria of what constitutes a generalized allergic reaction and many other things. It is therefore exceedingly difficult to estimate the frequency of deleterious reactions.

The use of enzyme-digested antitoxins, such as that prepared by Parfentjev,[25] has considerably decreased the number of reactions. Top and Watson[26] believes that this "despeciated" antiserum has reduced allergic reactions — formerly observed in about 40 per cent of cases — to less than 10 per cent in a large number of unselected cases. However, even with the use of these modified serums an irreducible minimum of reactions that is fairly high exists.

Greater Effectiveness of Tetanus Toxoid Prophylactically

Tetanus antitoxin when given at the time of an injury is usually effective in preventing tetanus. However, to ensure success, it is necessary to continue administering the antitoxin every ten to fourteen days until complete healing has taken place. This is usually not done, and in the majority of cases only a single dose is given, often resulting in a false sense of security. Practically every study of the illness reveals many cases in which tetanus antitoxin failed to prevent tetanus (Table 6). Particularly outstanding is the great number of cases mentioned by Kirschner[28] as occurring in the German forces in World War I, in spite of the administration of tetanus antitoxin.

Tetanus toxoid when properly and thoroughly administered provides almost complete protection. A review of the experience of the British Expeditionary Forces in the African and European theaters in World War II, presented by Boyd,[27] revealed that only 6 cases of tetanus developed in soldiers who had previously had over three inoculations of tetanus toxoid. In the American experience during the same war on all fronts, including the zone of interior as well as overseas, Long[29] found that only 12 cases of tetanus had occurred in the entire Army personnel. Of these, only 4 followed both the basic course of toxoid and the stimulating dose; 2 additional cases followed the basic course in which the stimulating dose was omitted. The United States Army procedure for immunization consisted of three 1-cc. injections of fluid toxoid at three-week intervals followed by a routine stimulating dose in one year and an "emergency" stimulating dose at the time of injury. The 12 cases in the American Army represent a frequency of 0.44 case per 100,000 wounded (0.22:100,000 if only the immunized are counted). Bruce[4] found that among unprotected personnel about 9 cases of tetanus per 1000 wounded occurred — that is, 900 per 100,000. On the basis of these figures toxoid is over 99.9 per cent effective. Bruce reported an incidence of about 1.12 per 1000 among men protected with prophylactic tetanus antitoxin.

TABLE 6. *Development of Tetanus in Spite of Prophylactic Administration of Tetanus Antitoxin.*

Author	Cases of Tetanus	Patients Receiving Tetanus Antitoxin	
		no.	percentage
Gessler[8]	121	11	9.1
Gruich[1]	289	3	1.04
Boyd[27*]	103	23	22.3
Vinnard[3]	352	10	2.8
Huntington[9]	642	72	11.2
Bruce[4*]	1,458	899	61.7
Kirschner[28]	—	20,000	—
Press	100	6	6.0
Totals†	3,065	1,024	
Average			33.4
Total nonmilitary	1,504	102	
Average			6.8

*Studies based on wounded military personnel.
†Exclusive of Kirschner's[28] cases.

Factors Against Routine Immunization

The factors against routine immunization are as follows: the relative rarity of the disease and the lack of communicability; the availability of antitoxin as a safeguard for injuries customarily causing tetanus; the reactions to tetanus toxoid; the cost of tetanus toxoid; and the possibility of preventing the majority of cases and avoiding in-

discriminate immunization of millions by limitation of active immunization to specially susceptible groups.

Relative Rarity and Lack of Communicability

Tetanus is definitely not a common disease in civilian life at present. In 1945 only 439 cases were reported in the United States.[30] Because the illness is not contagious, it can hardly be much of a public-health threat.

In examining these figures more closely, it was found that tetanus was not a reportable disease in four states and that, even in the states in which it was reportable, some cases were not being reported. This could be determined by the fact that more deaths due to tetanus were being reported in some areas than cases. Since death certificates were necessary for burial, this was understandable. Moreover, a large percentage of the deaths due to tetanus followed injuries, and when two or more diagnoses appeared on the death certificate the death was charged to the injury and not to tetanus. According to the *Manual of Joint Causes of Death* whenever tetanus coexists with accidental injuries including burns, cutting or piercing injuries, firearms or abortion, conditions of pregnancy, childbirth or puerperium, the death is not charged to tetanus but to the other cause.

A study by the National Office of Vital Statistics[31] reveals that in 1940 there were 560 certificates recorded in which tetanus was given as the primary cause of death. In an additional 350, it was listed as secondary. This gives a total of 910 tetanus deaths for that year. Assuming the case mortality to be 40 per cent, there should have been 2275 cases in 1940. However, only 411 cases were reported for that year. During the same year, deaths resulting from other diseases for which active immunization is available were diphtheria (1457 cases), whooping cough (2926 cases), typhoid fever (1378 cases) and smallpox 14 cases. As an item of additional interest, it may be noted that there were 706 deaths attributed to measles, 1026 to poliomyelitis and 1725 to acute rheumatic fever.[32]

Another factor opposing routine use of toxoid and related to the relative rarity of the disease is that tetanus fails to follow many injuries that might be expected to cause it. Everyone is familiar with the great many cases in which penetrating wounds or severe burns have failed to result in tetanus in spite of the absence of any precautions. In an attempt to estimate the frequency with which injuries fail to result in tetanus and also the proportion of injuries sustained for which the average well trained physician would give tetanus antitoxin, the following procedure was carried out. The records of 250 consecutive cases of accidental injuries treated in the outpatient department of a reputable metropolitan hospital in Boston were examined. During that time, 20 injuries were treated with tetanus antitoxin or tetanus toxoid. One hundred lacerated injuries severe enough to require suturing were not given tetanus antitoxin or toxoid, and 130 additional lacerations, abrasions and minor puncture wounds were treated that were not serious enough to merit either suture or any prophylactic measure for tetanus. During, and for an ample time after, this period, no patients with tetanus were admitted to the same hospital for treatment. This experience corroborated the belief that many injuries that are potential precursors of tetanus fail to result in tetanus in spite of the omission of prophylactic measures.

Some experimental work has been done in animals to indicate that the mere presence of tetanus spores in a wound is not sufficient to cause the disease. Other changes of some type are considered to be necessary for the spores to germinate. Space does not permit a detailed description of this work, but among the theories advanced are a change in oxidation-reduction potential of the tissue or tissue necroses, or both, and the presence of ionizable calcium salts.

The large number of human beings harboring tetanus bacilli in their intestines suggests the possibility of circulating antitoxin in the blood stream. This has been corroborated by Tenbroeck and Bauer,[33] who found the antitoxin in about 25 per cent of the persons tested, and also by Van der Reis.[34] This represents another possible factor in explaining the discrepancy between the plentiful distribution of tetanus spores and the scarcity of the disease.

Efficiency of Tetanus Antitoxin

There is ample scientific evidence that tetanus antitoxin, if given repeatedly at intervals of ten to fourteen days from the time of injury until complete healing, will prevent tetanus. This is available in practically every city and village in the United States wherever physicians are located. It does not apply, however, to injuries in which physicians are not in attendance or to those in which physicians do not use it.

Reactions to Tetanus Toxoid

Most of the relatively few adverse generalized allergic reactions were found to be due to Witte and Berna peptones, which were part of the culture mediums commonly used in the preparation of the toxoid. When these were removed, the number of reactions dropped considerably. For example, Long,[29] in a study of about 10,000,000 soldiers, found that the ratio of significant reactions dropped from 46:100,000 to less than 2:100,000. The recently reported crystallization of tetanus toxoid[35] gives promise of a toxoid practically free of any impurities and therefore even less susceptible to allergic reactions.

Cost of Tetanus Toxoid

The cost is the same for both alum-precipitated and fluid toxoid, varying from $1.12 to $1.60 per immunizing dose. This is the retail price to the patient. The analogous price of tetanus antitoxin is from 45 to 85 cents. The cost and ease of administration would be reduced if the tetanus toxoid were combined with another toxoid.

Limitation of Active Immunization to Specially Susceptible Groups

If one can assume that the majority of cases of tetanus result from injuries sustained in and around barnyards, ranches and in the proximity of grazing animals, it seems feasible to limit immunization to this group, as well as military personnel. Unfortunately, this assumption is not warranted, as pointed out above.

Summary and Conclusions

An attempt has been made to present impartially the evidence for and against routine active immunization for tetanus. Several of the facts noted are contrary to current general opinion. It was found that about 50 per cent of all injuries leading to tetanus in the civilian population were exceedingly trivial or completely unknown. In addition, it was noted that the majority of bacteriologic studies revealed that tetanus spores were very widely distributed and more frequently found in human feces than in those of horses.

It was noted that the mere presence of tetanus spores in a wound was not sufficient to cause the disease, and the discrepancy between the amount of injuries capable of resulting in tetanus and the number of cases actually occurring was stressed. Several possible explanations for this, including evidence for the existence of a natural immunity, were mentioned.

Statistical evidence was demonstrated to show that less than 20 per cent of the cases of tetanus are reported in the United States. There were at least 910 deaths due to tetanus in the United States in 1940. This compares with 1457 due to diphtheria, 1378 to typhoid fever and 706 to measles.

It was further pointed out that in addition to the number of cases and deaths due to tetanus, one must take into account the number of people sensitized to horse serum by prophylactic tetanus antitoxin as an explanation of the small number of fatal cases. It was estimated that well over two million doses of tetanus antitoxin are given annually and that at least a seventh and probably much more of the entire population receive one or more doses during life. However, if past concepts of proper treatment of injuries are carried out — that is, tetanus antitoxin for penetrating injuries and severe burns — about a third of the population should receive tetanus antitoxin. If present knowledge of the distribution of tetanus spores and the type of injuries associated with the disease were generally publicized, the problem would be greatly intensified. The conscientious physician, aware of the widespread distribution of tetanus spores, knowing the potentiality of tetanus with trivial injuries and being unable to determine which cases might go on to develop it, would be forced to give tetanus antitoxin for nearly all injuries. In view of the definite effectiveness of tetanus toxoid and its almost complete freedom from adverse reactions, its use seems to be indicated.

The not infrequent failure of tetanus antitoxin prophylactically is indicated by the fact that about 7 per cent of civilian and over 50 per cent of military cases developed in spite of its use.

To avoid the increased risk of anaphylaxis and the more frequent allergic reactions to repeated doses of tetanus antitoxin, it is advisable to give toxoid concurrently with each inoculation of tetanus antitoxin. If this active immunization is then completed, it should be unnecessary to use antitoxin for any future injuries in a person by then sensitized to horse serum.

It is my opinion that active immunization against tetanus as a practical public-health measure is indicated. Until further information regarding the pathogenesis of the disease or a simple method of estimating the natural antitoxin level is available, it should be given routinely by private physicians and should also be included in health-department programs for all children. The toxoid should be given to children combined with diphtheria or pertussis vaccine, or both. In addition, children who have been immunized for diphtheria and pertussis, but not for tetanus, should have tetanus toxoid available and be encouraged to use it. Adults with increased accident hazards, such as manual laborers in both rural and urban areas, should also be immunized.

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PAPILLARY CYSTADENOCARCINOMA OF BOTH OVARIES

Report of a Case with Apparent Cure Eight Years after Operation

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THE following case appears to be one of those mysterious cases that cannot be explained. After reading textbooks and journals I came to the conclusions that the patient had had actual surgical treatment four years after the onset of symptoms, that she had not been given x-ray therapy and that a hysterectomy had not been performed.

Meigs[1] states that cancer of the ovary of the malignant papillary cystadenoma type is about as malignant as any other epithelial growth and that bilateral oophorectomy and hysterectomy are the proper treatment. Jones[2] reported 30 cases of papillary cystadenoma of the ovary and stated that the prognosis is extremely poor. Another authority, Pemberton,[3] writes that cancer of the ovary should be treated by as radical an operation as circumstances permit, followed by x-ray therapy. The results of treatment are poor, and early diagnosis is essential.

Curtis[4] states that prognosis with frank carcinoma of the ovary is not good. Five-year salvage is obtained in 60 per cent of the patients with unilateral growths and in 20 per cent of those with cancer of both ovaries, but this includes many small early cancers discovered at operation and cases with slowly developing tumors and relatively benign peritoneal implants.

The comments of other authorities indicate that upon the advent of such symptoms as discomfort, pain or free fluid in the abdomen, the patient is very seriously handicapped and that the chances of recovery are extremely poor.

A. S., a 26-year-old housewife, entered the Margaret Pillsbury General Hospital on November 7, 1939, complaining of discomfort in the lower abdomen, distention, menstrual irregularity and loss of weight, as well as pain in the lumbar region and legs.

The past and family histories were irrelevant. The patient was married, and her husband was well. She had had no pregnancies. For 1 year prior to admission she had complained of some discomfort in the lower abdomen, back and legs. During the last 2 months before admission the discomfort increased markedly, and since other distressing symptoms appeared, admission was advised.

Physical examination showed the patient to be pale and cachectic. The abdomen was distended and tender, and on percussion the presence of fluid was detected. No masses were felt. Pelvic examination revealed a small uterus in normal position, not movable, and a tender, diffuse mass in the pelvis. A tentative diagnosis of tuberculous peritonitis or adenocarcinoma was made.

Examinations of the blood were within normal limits. The urine showed a trace of albumin, sugar and acetone.

On November 9 a laparotomy was performed, and about 2 liters of straw-colored fluid drained from the abdominal cavity. Exploration of the pelvic cavity revealed a small uterus in good position and large papillary growths of both ovaries, with extensive papillary peritoneal implants in the entire pelvic cavity.

Three other physicians were called in for advice, and it was decided that the disease was too extensive and advanced for surgery to be of any benefit. A biopsy was taken, and the abdomen was closed.

The pathologist reported metastases of a papillary cystadenocarcinoma of the ovary. The patient was discharged on November 22, still complaining of some abdominal discomfort.

On December 2 the patient was seen at home. She complained of severe abdominal distress and distention; she had

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had no bowel evacuation for 2 days and had expelled very little flatus. Intestinal obstruction was feared, and she was admitted to the New Hampshire Memorial Hospital on December 3. From that time to the day she was operated on for the second time she was treated as a hopeless case. Consultants advised taps and morphine and believed that x-ray therapy would be of no help. The patient was treated accordingly until about June 1, 1942. She was tapped 63 times and from 5000 to 10,000 cc. of fluid removed every 2 or 3 weeks. She was kept comfortable with morphine, the dosage being increased to 30 mg. every 3 hours.

The patient at that time begged to be operated on again, no matter what the outcome might be. The only intention was to explore and insert a mushroom catheter to relieve her of further taps. On June 1 she was operated on at her request. Her weight was about 80 pounds. The abdomen was opened, and there were no peritoneal implants. A fair amount of straw-colored fluid was found. The appearance of the pelvis was altogether different. All the papillary growths were encapsulated in one large mass to the left and two other smaller ones to the right. All were adherent to the adjacent organs, rectum, uterus and bladder. The growths were dissected and removed with great difficulty except for a small portion about the size of a silver dollar in the right fossa. Some of the contents were spilled in the abdominal cavity and removed with care. The uterus was not removed because of the difficult and long operation. One mushroom drain was left in place, and the abdomen was closed in the usual way.

The pathological diagnosis was papillary cystadenocarcinoma of both ovaries (Fig. 1), with extension to the peritoneum.

The postoperative recovery was fair and rather stormy because the patient was deprived of morphine. She was given two 500-cc. transfusions. The drain was removed on June 27. The abdomen was not healed before September 12, and until that time the temperature went as high as 102°F. The patient was then transferred to the medical service. She improved, gradually gained weight and was discharged November 22, after having spent 1086 days in the hospital.

The patient has been checked regularly every 6 months. She had one scant menstrual period and occasional hot flashes after the second operation. She was checked for the last time 2 months ago, with no apparent recurrence. Her weight is now 140 pounds; she feels well and works every day.

When Dr. George Van S. Smith, of Brookline, Massachusetts, was told about this case in 1946, he thought that there might have been an error in the pathological diagnosis, but after studying the slides himself, he was convinced that the diagnosis was correct and that the case was out of the ordinary and difficult to understand and explain.

Summary

Papillary cystadenocarcinoma of the ovary is a malignant epithelial growth. The prognosis is very poor. Early diagnosis is essential, and treatment should be as radical as circumstances permit, followed by x-ray therapy.

A case of papillary cystadenocarcinoma of the ovary, diagnosed approximately one year after the onset of symptoms, is reported. The patient had actual surgical, but not radical, treatment four years after the onset of symptoms and without postoperative x-ray therapy. Yet after more than eight years she feels well, works every day and is apparently cured.

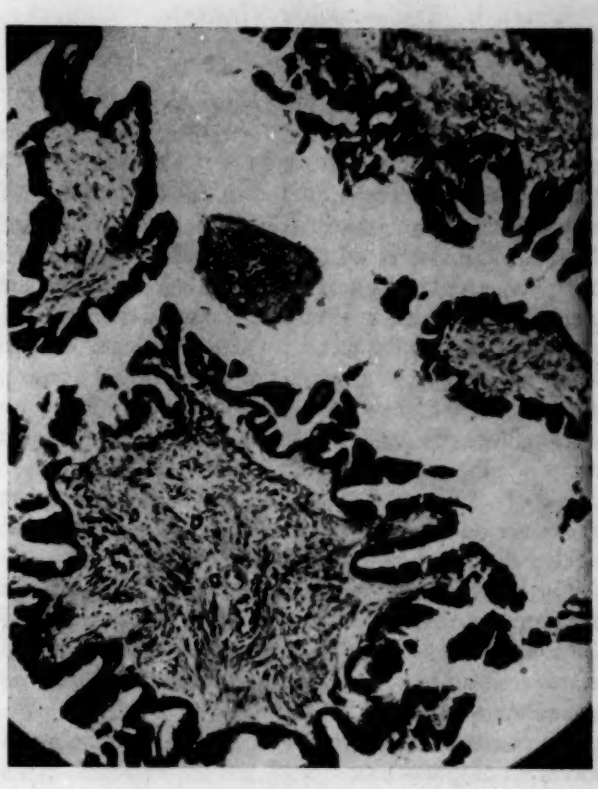

FIGURE 1. *Photomicrograph of Section of Ovary, Showing Papillary Cystadenocarcinoma.*

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MEDICAL PROGRESS

MALARIA (Concluded)*

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TRANSFUSION MALARIA

Unexpected clinical malaria has occurred in many nonendemic malarious areas when patients receive transfusions of blood from donors who had previously lived or had been exposed to infection in endemic malarious areas.[54–58] In New England the majority of such cases of transfusion malaria before World War II resulted from transfusions from adults who had previously lived in the Mediterranean area. With few exceptions, quartan malaria was the type that was contracted by the recipients of such donor blood. Rubenstein et al.[59] recorded some of these cases, which were reported to the Massachusetts Department of Public Health. In the list of cases, only two of the twelve infections were caused by *Plasmodium vivax*. With the exception of one unidentified case, the other cases were definitely identified as quartan malaria.

The basic reason for the incidence of quartan malaria among these cases resulting from transfusion is the long-lived latency of this type of malaria. This characteristic is not typical of *P. vivax* or of *P. falciparum*.

Two results of World War II and increasing air travel to tropical areas have tended to focus attention on this problem of transfusion malaria. In the first place, relatively great numbers of men were stationed at one time or another during World War II in endemic or hyperendemic malaria areas. In the second place, blood banks have been organized at hospitals for transfusion purposes. This blood is stored for varying periods up to two weeks before it is used.

Although very little quartan malaria occurred in the armed forces during World War II, the high incidence of *P. vivax* and *P. falciparum* prompted a review of the danger involved in using blood from such persons after they have had malaria. *P. falciparum* is not a seriously relapsing type of malaria, and it tends to be cured or to stop spontaneously within a year after the initial infection, provided there is no reinfection or transmission by mosquitoes. On the other hand, the vivax malaria that occurred among the forces in the Pacific theater of war was a seriously relapsing type. There are still a number of these men who continue to have relapses although they had their initial infection two to four years previously. Available records show that vivax malaria seldom persists beyond three to six years after the initial infection. Thus, blood for transfusion purposes should be refused even in cases of emergency from persons who have given a previous history of any type of malaria. If the species causing the previous infection were known, this statement could be modified, but the intended donor seldom knows more than that he had malaria. It must be realized that the blood during the intervals between relapses of vivax malaria is infective and should not be used for direct transfusion or for storage in blood banks. There is no reason, however, to exclude persons with a previous history of malaria from giving blood for the production of plasma.[60] The parasites live within the red cells, and these cells are discarded during the processing of the plasma for therapeutic use.

The incubation period for transfusion malaria depends upon the numbers of parasites present in the donor's blood and the species of plasmodium. The incubation of quartan malaria as passed by inoculation of infected blood to paretics ranges from one to four weeks. Thus, with submicroscopic parasitemia existing in latent malaria, the incubation period might be as long as three months. This is not so, however, with *P. vivax* from patients who have had relapses of tertian malaria within a few months. In these cases, there are greater numbers of circulating parasites and hence the incubation period in the recipient would be five to fourteen days.

Thus, it should be emphasized that donors of blood for transfusion or for the replenishment of supplies in the blood bank should be asked about a previous history of malaria. If they have had malaria at any time in the past or recall symptoms that might have been due to malaria, their blood should be refused. Their blood can be used, as stated above, for the production of plasma.

INDUCED MALARIA

The paradox of using one disease therapeutically to treat another exists in the practice of using human malaria to obtain hyperpyrexia in patients with paresis or neurosyphilis. This therapeutic procedure dates from the successful experiments of Wagner–Jauregg in 1917.[48] The effects of hyperpyrexia produced by induced malaria, mechanical fever cabinets or typhoid vaccines in the hands of many clinicians appear to favor the use of malaria.

The discovery of penicillin, however, and its efficiency in the treatment of paresis was originally believed sufficient to supersede and eliminate the

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need for therapeutic malaria. This belief has not been substantiated by results of extensive series of treatments using penicillin alone.[61]

The mode of action of malaria therapy and of penicillin on *Treponema pallidum* is not known. Since penicillin has no effect on either malarial parasites or clinical malaria, malarial and penicillin therapy either given simultaneously or in sequence have been used extensively.[61] That these procedures will continue to be utilized for some time is entirely possible in view of the 5 per cent increase of syphilis reported for the first half of 1947[61] and the expected subsequent increase in neurosyphilis. Thus, a brief review of procedures for handling therapeutic malaria is warranted.

The infection of choice for therapy of white patients is *P. vivax*. Various strains, such as the McCoy, St. Elizabeth's[62] and Chesson,[63, 64] are generally available for therapy. Except for the use of infected anopheline mosquitoes to produce experimental infections, the infection is induced in man by passage of 2 to 5 cc. of infected blood, and the incubation period, depending on dosage, is approximately two to six days. Wherever reliable parasite counts can be obtained, definite dosages give more consistent incubation periods and predictable course of infection. Kaplan et al.[65] recommend a dosage of 1,000,000 *P. vivax* parasites for susceptible white patients. In our experience with the McCoy and St. Elizabeth's strains,[66] a dosage of 500,000 parasites per kilogram of body weight gives desirable results. There is also evidence that the compatibility of the parasitized blood to be inoculated affects the incubation period. When compatible blood is used the incubation period is approximately two days shorter.[64] The determination of parasite densities during the infection helps also to predict onset, clinical course and spontaneous control of parasitemia.

American Negroes have varying degrees of natural resistance to certain but not all strains of benign tertian malaria.[67] Hence, if Negroes fail to develop clinical malaria after inoculation with *P. vivax*, quartan malaria (*P. malariae*) should be used to obtain the desired hyperpyrexia. If available, the latter species should be the original organism of choice for Negroes. This infection has some disadvantages, such as a longer incubation period (given variously as twelve to fifteen days[68] in a series of 92 patients and as an average of slightly over nineteen days in a series of 38 patients[69]) and intervals of seventy-two hours between paroxysms. These characteristics lengthen the time of hospitalization considerably and tend to eliminate the use of quartan infection in other than resistant Negroes and white patients.

P. falciparum of malignant tertian malaria is considered too dangerous for use in treating paretics without laboratory control. This type of malaria is less severe in Negroes than in white patients, and it can be used to obtain hyperpyrexia without great risk if the parasitemia is not allowed to exceed approximately 100,000 per cubic millimeter. If this infection is used in paretics, parasite densities should be determined at least twice a day because of the rapidity of multiplication of the parasite during the primary attack.

In numerous hospitals, the supply of paretics is not great enough to ensure continuous passage of malaria. Since infected blood loses its viability within two weeks when stored at ordinary refrigerator temperatures, the problem of keeping and obtaining infected blood for new patients constantly arises. The technic of using low-temperature freezing to preserve human malarial parasites has been developed.[66, 70] The method was originally devised for the preservation of simian and avian plasmodia.[29, 71, 72] If a dry-ice cabinet or a mechanical deep freeze is available to maintain the temperatures below —50° C. infected blood containing *P. vivax* or *P. falciparum* can be frozen and stored for lengths of time up to at least six months. Attempts have been unsuccessful with *P. malariae*. One or two cubic centimeters of the infected blood is sealed in thin-walled, 5-cc. vials or ampoules and frozen quickly by twirling of the vials in a bath of alcohol precooled to —50°C. or below or in a bath of dry ice and alcohol at a similar temperature. At no time should the temperature of the stored blood be allowed to rise above —50°C. In use, the vials of infected blood are transported from the storage cabinet in a bath of alcohol and dry ice (—50 to —70°C.) to the bedside where it is to be used. The vials of blood are thawed quickly in water at 37°C., a syringe is filled, and the blood is injected immediately. Two to five cubic centimeters of thawed blood has been injected without any reaction. In our laboratory, at the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, where human and simian parasites are maintained constantly in a deep-freeze, best results have been obtained with blood taken during the last half of the cycle before a paroxysm, when the parasites are half or full grown. Sterile precautions and sterile equipment must be used throughout the procedure.

In the previous review,[1] the use of thiobismol was discussed as an aid in inhibiting one of the paroxysms in debilitated patients who have daily rises in temperature during *P. vivax* infections. Many inquiries have been received about this procedure. When the directions for its use as recommended by Young, McLendon and Smarr[73] are followed, desired results are obtainable. But when thiobismol is injected at the wrong part of the parasite cycle, the results are disappointing. No information is available about the exact mode of action of this drug on *P. vivax*, but it is known that the half-grown parasites or trophozoites are affected. Thus, to derive maximum effects, 0.1 to 0.2 gm.

of the drug is injected intramuscularly sixteen to twenty-eight hours after the last paroxysm. Also, this drug appears to be effective only in inhibiting *P. vivax* and not *P. malariae* or *P. falciparum*. Kaplan, Read and Becker[74] have studied the action of thiobismol in therapeutic quartan malaria more recently. This study shows that the drug has a predictable action in reducing the frequency of paroxysms in double or quotidian quartan malaria if the parasitemia prior to injection is below 10,000 per cubic millimeter. Again the drug was not effective on young or mature parasites. The absence of laboratory control of infections in most hospitals and the unpredictable interruptions of paroxysms when injections are not properly timed with the parasite cycle make the use of thiobismol against quartan infections impracticable.

Chemotherapy

Advances in the chemotherapy of malaria are almost entirely the result of an extensive wartime research program. The program was dictated by the necessity of fighting in malarious areas and by the urgent need of prophylactic and curative drugs that would offset the grave loss of the source of quinine from the Netherlands East Indies. Although the losses from World War II are beyond calculation, mankind will benefit for years to come by the vision, skill and co-operation of American and British workers, who demonstrated how to use quinacrine most effectively, who synthesized and tested thousands of drugs and who proved the value of new antimalarial drugs.

Therapeutic problems with malaria involve the need of a drug to act as a prophylactic preventive of infection by killing the infective stages, or sporozoites, injected when the mosquito bites or by preventing the parasites from entering and from developing in the blood stream to cause the disease. In benign tertian malaria, a drug to be of specific value must produce not only a clinical cure but also a radical cure by destroying the hypothetical tissue stages of parasites that are responsible for relapses. The same requirement applies to drugs needed to produce a radical cure with latent malaria (*P. malariae*).

As previously stated[1] there was no agreement among clinicians in malarious areas about the dosage of quinine and quinacrine to be used in the treatment of malaria and about the results. It should also be pointed out that the dosages then in use for man were largely arrived at on empirical grounds. Little was known about their fundamental pharmacology, range of tolerance, most effective dosage schedules, mode of action on parasites and strain susceptibility to the two drugs.

Quinacrine

At the beginning of World War II, quinacrine was the most effective antimalarial drug available. The drug had an unfortunate reputation for toxicity, and no large quantities were being produced. Fortunately, the results of a concentrated pharmacologic and clinical testing program, combined with pharmaceutical skill, which enabled the manufacture of great quantities of this drug, made the difference between success and failure of military operations in tropical and subtropical theaters of war. New drugs were produced before the end of the war, but screening for antimalarial properties by animal injections, clinical testing, field trials and manufacture consumed too much time to make them a factor in field operations. Perhaps they can now be considered weapons to benefit the public health in peace.

The extensive synthesis of new compounds and the pharmacologic and clinical testing program in this country have been documented.[75] The broad organization that guided the emphasis and reasoning of the research projects will not be discussed here. The contributions, the majority of which are still unpublished, are so numerous that they can be discussed only briefly. To the discussion will be added the antimalarial studies and discoveries of British investigators that are of interest and practical application to clinicians.

Extensive pharmacologic, clinical, laboratory and field studies have made quinacrine one of the better known drugs. The pharmacologic behavior, advantages and disadvantages of this antimalarial agent are now known. The studies of Shannon and his collaborators[75–78] showed that the efficacy of quinacrine as a suppressive and as a clinical cure for malaria depended upon the plasma concentration of the drug. Analyses of blood concentration in man after the previously recommended dosage schedules revealed the difficulty and inadequacy of obtaining effective blood levels quickly. However, when a priming or loading dose of the drug was given on the first day, high plasma concentrations were obtained more quickly. The dosage is then lowered on the second day, and the required level can easily be maintained to complete the course.

Thus, the recommended therapeutic dosage of quinacrine for clinical malaria in adults is now two tablets of 0.1 gm. (a total of 3 gr.) and 1 gm. (15 gr.) of sodium bicarbonate by mouth every six hours for five doses and then one tablet of 0.1 gm. three times daily for six days (total dosage, 2.8 gm. in seven days).[79] Each dose should be taken with a full glass of water, sweetened tea or fruit juice after a meal to avoid gastric discomfort.

The principles involved with the correlation of plasma concentration for suppressive or therapeutic effects have been questioned.[80] Available data show that on the basis of plasma concentration quinacrine is over a hundred times more active than quinine. On the basis of oral dosage quinacrine is only three times more active. Thus, dosage schedules appear, in the words of Marshall,[80]

"to have more meaning than that based on plasma concentration."

Studies by another research unit of the Army[81] tend to oppose this view. This group determined the range of plasma concentrations, obtained in a group of men on various dosage schedules, concentrations after completion and after interruption of drug courses, the variation of concentration in persons on the same schedule, the influence of environment on the plasma concentration and the toxicity of the drug. The important results for this discussion are the wide variations of plasma concentrations obtainable in a group on the same dosage schedule and the relative nontoxicity of the drug.

Fairley and his collaborators[82] in Australia studied the build-up, equilibrium level and die-away concentrations of quinacrine after certain dosage schedules, and the effect of such levels on suppression and clinical and radical cure of benign tertian and malignant tertian malaria. These studies established the fact that quinacrine in a dosage of 0.1 gm. (1½ gr.) daily suppressed falciparum malaria. When the dosage was continued for a required period of approximately a month after the last exposure to infection, a radical cure was obtained. The dosage schedule, furthermore, suppressed benign tertian malaria, but clinical malaria will develop at varying intervals of a few days up to a year[83] after the drug has been discontinued. The prophylactic or suppressive dosage for adults is as follows: one tablet of 0.1 gm. (1½ gr.) daily, preferably beginning two weeks in advance of exposure, and continuing for at least four weeks after the last possible exposure in a malarious area.[79] When quinacrine is to be taken as an antimalarial drug, administration should be started up to two weeks before a malarious area is entered. This procedure is essential to get an effective plasma level for suppression of clinical malaria.

The thorough review of toxicity of this antimalarial agent by Findlay[84] deserves comment. A comprehensive reference list was covered to record the severe toxic reactions associated with quinacrine therapy before and during the war. This paper should be read by those passing on claims for compensation or pension by persons who have a history of toxic effects following quinacrine therapy.

The primary toxic reactions to quinacrine involved the skin, central nervous system, hematopoietic system and eyes. Lichenoid dermatitis contracted by American and Australian troops in the Pacific area is considered in detail. The incidence of toxic psychoses, frequently exaggerated during the war, was found to be quite low. In a collected series of 89,168 persons receiving quinacrine, 126 developed psychotic symptoms. Unique corneal lesions are described that developed in a small series of industrial workers handling the drug in quantity and in persons taking large doses of the drug.

The author emphasizes the fact that "hundreds of thousands of persons in the services were given quinacrine without ill effects."

Chloroquine

Another compound, chloroquine diphosphate (synonyms, SN-7618, resochin and aralen) has been found to be a more potent antimalarial drug than quinacrine.[85] This compound—7-chloro-4 (4-diethylamino-1-methylbutylamino) quinoline diphosphate) — was first synthesized and patented in Germany.[86] Two years later the patent granted in this country was assigned to Winthrop Chemical Company. During the North African Campaign, sontochin (SN-6911), a relative of chloroquine, was captured from the Germans, who were using it against malaria. This led to an extensive investigation of both drugs in this country.

Surrey and Hammer[87] synthesized samples of chloroquine and sontochin for testing, and additional samples were synthesized later by "several University laboratories under OSRD contract."[75, 86] Screening tests with avian malaria and extensive pharmacologic, clinical and field tests showed that both drugs had valuable antimalarial properties but that chloroquine was superior, with approximately the same antimalarial properties as quinacrine. The rapidity of absorption and lesser localization of chloroquine in tissues and organs contributed to the greater potency on lower dosage schedules and hence with lower plasma concentrations. One dose of chloroquine per week (0.5 gm.) will suppress *P. vivax* and *P. falciparum* infections, and clinical malaria can be treated successfully in three to five days. Furthermore, the drug does not lead to discoloration of the skin. The toxic symptoms developing from therapeutic dosages parallel those of quinacrine. Mild and transient headache, visual disturbances, pruritus and gastrointestinal disturbances are the most common complaints. In the words of Loeb et al.,[85] "none of these manifestations have been constitutionally serious and all have been readily reversible."

Most and his associates[88] treated more than 1000 cases of acute vivax malaria, and compared the control of symptoms and toxicity by quinine, quinacrine and chloroquine. As might have been expected, each drug gave different results, but in general chloroquine controlled fever more quickly, reduced the parasitemia faster, lengthened the interval between relapses and gave less toxic symptoms.

Chloroquine will effect a complete cure of malignant tertian malaria. When taken prophylactically, this drug will not prevent infection, but it is effective as a suppressive. Clinical cures of vivax malaria are readily obtained, but relapses are not prevented.

The effective dosage of chloroquine (aralen) for suppression of malaria is 0.3 gm. of the base, but the manufacturers produce the drug as a diphosphate in tablets of 0.25 gm., and hence 0.5 gm. (two tablets of 0.25 gm.) in a single dose once in a week is recommended.[88, 89] In clinical malaria, an initial dose of 1 gm. followed by an additional 0.5 gm. in six to eight hours and then a single dose of 0.5 gm. on each of two consecutive days is recommended.[88, 89] (The total dosage of 2.5 gm., or ten tablets of 0.25 gm. each, in three days is higher than that used by Most et al.[90] — 1.5 gm. — for acute vivax malaria, but the higher dosage is calculated to make allowance for the salt content of the commercial preparation.)

Paludrine

An entirely different type of antimalarial drug was discovered during the war by British investigators and announced in 1945.[91, 92] This drug, originally called paludrine (synonyms-M-4888,SN-12,837 and chlorguanide hydrochloride),[75, 93, 94] represents another milestone in the efforts of man to find an ideal drug for true causal prophylaxis and treatment of malaria.

A series of researches[93] was initiated in an effort to explore compounds with different ring structures that would give antimalarial activity against the tissue stages of the parasites. The pyrimidine compounds were selected because of the need for this ring structure as a building block for nucleoproteins and because of the importance of nuclear components for cell growth and multiplication. The chance that analogues of essential pyrimidines might interfere with growth in the way that sulfonamides interfere with utilization of para-aminobenzoic acid seemed worth investigation.

Anilinopyrimidines were prepared and tested and the compound "2666" was found to have antimalarial activity against *P. gallinaceum* in chicks. After the synthesis and testing of many more compounds, it was found that compounds containing a guanidine group and without the pyrimidine ring exhibited outstanding antimalarial properties. Thus, the new drug N_1-p-chlorophenyl-N_5-isopropylbiguanide acetate, called paludrine, was developed.[95] The salt of this drug now in use is the hydrochloride.

This drug was screened against four species of avian plasmodia and then tested in England[96, 97] and Australia[98, 99] against types of malaria in human beings. The clinical testing in Australia involved 200 volunteers infected with the highly virulent New Guinea strains of parasites. The results of clinical trials in this country have not been published, but reports of more recent field trials are beginning to appear. The results of comparative trials with chloroquine and paludrine under identical conditions and in a variety of patients of different age groups will be awaited with interest.

The prime advantage of paludrine over other antimalarial drugs is that it is a true causal prophylactic for falciparum malaria, giving complete protection against this parasite when the proper dosage is taken. The drug will also give radical cures of this lethal type of malaria. Although the drug will suppress and give clinical cures of vivax malaria, relapses will occur. The drug acts against the hypothetical tissue stages of falciparum malaria and against the asexual stages of *P. falciparum* and *P. vivax* in blood that are responsible for the clinical symptoms. The action against the circulating stages consists of prevention of multiplication and sterilization of gametocytes so that they cannot develop into infective stages in the anopheline mosquito. The rapid excretion of the drug within forty-eight hours[100, 101] and its failure to stop gametocyte production in falciparum malaria[99, 102] are disturbing findings that need more complete investigation.

The toxic dose is approximately two hundred times the therapeutic dose, so that the drug is relatively harmless. Dosages over 1 gm. daily may give rise to gastrointestinal disturbances such as vomiting, abdominal pain, diarrhea and urinary symptoms including hematuria, sheets of epithelial cells and hyaline or granular casts. The symptoms subside when the drug is discontinued.[94, 99]

The dosage for causal prophylaxis of *P. falciparum* infection is 0.1 gm. twice weekly. A single dose of 0.3 gm. once weekly is usually effective in suppressing clinical symptoms and parasitemia of both malignant and benign tertian malarias. In a radical cure of falciparum malaria, 0.3 gm. once daily for ten days is usually effective. For vivax malaria, the same dosage may be employed, but no radical cure can be obtained and clinical improvement is very much slower than that after administration of quinacrine or chloroquine. Viswanathan and Bailey[102] treated 8 patients with quartan malaria and found that the temperature persisted from two to five days after the first dose of the drug, which was in contrast to the short duration of temperature and parasite prevalence in falciparum malaria. More field trials are needed before the efficacy against quartan malaria can be assessed.

Pentaquine

Before World War II, the only drug that was effective against the gametocytes of *P. falciparum* was plasmochin (synonym, pamaquine). The relatively low relapse rate with vivax malaria after combined therapy with plasmochin and quinine had been noted by a number of investigators in India and Panama.[103] Although plasmochin was included in the initial recommended therapy for malaria by the Army, high toxicity and little need for gametocidal properties caused its use to be discontinued.

When great numbers of relapsing vivax malarial infections developed during the Pacific war, the extent and seriousness of the problem led to a reconsideration of the properties of existing antimalarial drugs. The revised dosage schedule with quinacrine provided radical cures with falciparum malaria, but the relapse rate with vivax malaria was not affected. Thus, plasmochin combined with quinine was the only known therapy that lowered relapse rates of vivax malaria. The high toxicity of plasmochin prevented its general use, but Most et al.[104] and Warthin and his co-workers[105] have used the combined plasmochin-quinine therapy to reduce relapses in vivax malaria. Nevertheless, less toxic analogues were sought. That search has now resulted in the discovery of two new and less toxic 8-aminoquinoline compounds[106, 107] called pentaquine (SN–13,276) and SN–13,274. The latter drug has not been named officially, but the name isopentaquine has been suggested.[107] These drugs when used singly in combined therapy with quinine are said to reduce the relapse rate of vivax malaria by 85 per cent. The compounds are not commercially available at the time of writing, but they should become available in the near future.

The recommended dosage applies only to clinical and radical cures of vivax malaria with pentaquine and quinine. The drugs are too toxic for suppressive or prophylactic use. "A daily dose of 60 mg. base (equivalent to 80 mg. of diphosphate) and 2 gm. of quinine administered concurrently" in divided doses every four hours for fourteen days is sufficient to produce radical cure of severe infections due to *P. vivax*. The drug is to be given only under close medical supervision and in a hospital if possible.[106]

Thus, we now have new drugs for the prophylaxis, suppression and treatment of malaria. Each drug appears to have special attributes against certain species and stages of plasmodia, but no drug answers the ideal requirements. The evidence is not sufficient to offer a final evaluation of any one of the new drugs. Furthermore, the claims made by some clinicians or malariologists will probably be discredited later by others. When those who test new drugs realize that malaria occurs in many races of people having different body weights, habits and diets, and natural or acquired immunity, the results of clinical trials can be compared more readily. The conditions of trial in various parts of the world are also dissimilar. Thus, to avoid controversy when results are compared, the many and varying factors of the drug tests should provide the foundation for interpretation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 34281

PRESENTATION OF CASE

A twenty-seven-year-old housewife entered the hospital because of abdominal swelling.

The patient had felt well until ten days before admission, when she began to notice abdominal swelling and nausea. Five days before admission she had pronounced abdominal fullness with vomiting, belching and passage of flatus. She was unable to take solid food.

She had been married five years and had two children. In the past three years she was unable to become pregnant. Her menstrual periods were regular until six months previously, when she skipped two menses and then had a heavy flow, and two weeks previously, when she missed her expected period.

There was no history of fever, jaundice or edema of the ankles.

Physical examination disclosed a well developed woman in no distress. The chest was clear. There was slight elevation of the right leaf of the diaphragm. The abdomen was enlarged, and there were generalized tenderness and shifting dullness. Pelvic examination revealed a soft, poorly defined, rounded mass in the left fornix. The uterus was freely movable, and there was no tenderness.

The temperature, pulse and respirations were normal. The blood pressure was 115 systolic, 70 diastolic.

Examination of the blood revealed the patient to be Rh+. The hemoglobin was 12.2 gm., and the white-cell count was 8900, with 71 per cent neutrophils. The total serum protein was 4.91 gm. per 100 cc., with an albumin-globulin ratio of 1:90. The prothrombin time was 26 seconds (control, 17 seconds). The chloride was 99 milliequiv. per liter, and the nonprotein nitrogen 18 mg. per 100 cc. A van den Bergh reaction was normal, a cephalin-flocculation test was ++ in forty-eight hours, and the bromsulfalein test showed 4 per cent retention of the dye. A blood Hinton test was negative. The stool gave a negative guaiac test.

X-ray examination revealed at least two rounded shadows of increased density in the right lung and another in the left and a small amount of fluid in the right pleural cavity. In the abdomen there was an area of hazy density apparently due to fluid, and a shadow suggesting the possibility of a mass in the pelvis. A gastrointestinal series was negative.

By the third hospital day the abdominal girth had increased from 91 to 96 cm., and there was a greenish discoloration in the umbilicus. An abdominal paracentesis yielded 4 liters of bloody fluid, with a specific gravity of 1.024, and a total protein of 3.73 gm. per 100 cc. Cytologic examination disclosed 777,200 red cells, 560 polymorphonuclear leukocytes and 20 lymphocytes per cubic millimeter. By the fifth hospital day the hemoglobin was reduced to 7.5 gm., with a red-cell count of 2,480,000, and later to 6.6 gm., with a red-cell count of 2,200,000 and a white-cell count of 4500. A mouse test of the urine for pregnancy was positive. By this time the patient was beginning to have a low-grade fever. She was given two successive transfusions, and an operation was performed on the twelfth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JUDSON A. SMITH: Let us pause to analyze the menstrual history. Although it is inadequate we can perhaps make certain deductions from it. In the first place, the fact that the patient had missed two periods six months previously

suggests that she could have been pregnant. She then had a heavy flow. How long that lasted, whether she assumed that that was a menstrual period, or whether it was accompanied by pain, we do not know. Presumably it means that she had a very diffuse period and then had re-establishment of the menses, because nothing is said about further irregularity of bleeding until finally she is said to have missed the last period. In other words, two weeks before admission she was due to have a period but did not have one. What could have become of this pregnancy, if she were pregnant? It seems unlikely that she could have had an abortion of a living two months' fetus during the "heavy flow," because that would have impressed her sufficiently for her to have reported it as a miscarriage. She could, however, have had a blighted ovum and completely aborted it during the period of "diffuse flowing." It seems rather unlikely that she could have had a so-called missed abortion — that is, a blighted ovum that remained in the uterus; otherwise we would not expect her to have had re-establishment of periods, which we are assuming although it is not so stated.

She could also have had a tubal pregnancy six months earlier, which ended with the death of the fetus. That might well be followed by a profuse flowing and then by re-establishment of the menses. One can hardly believe that she terminated a tubal pregnancy with tubal abortion or tubal rupture because there is no history of pain or shock or anything of that sort. I think we can be quite sure that, whatever sort of pregnancy she may have had then, the fetus did not go on growing. As for the recently missed period, she was about two weeks overdue, and we will leave the possible significance of that until later. I notice that no information about the size of the uterus is given. Is there anything in the record about its size? Presumably it was not particularly enlarged or, I suppose, it would have been mentioned.

Dr. Daniel S. Ellis: Dr. Meigs did a pelvic examination after the fluid had been withdrawn, but he did not think the uterus was abnormally large; this mass in the left vault was something very vague.

Dr. Smith: I do not believe that the laboratory work has much bearing on the diagnosis. I see, however, that there is no report on the urine examination; presumably, it was negative since nothing is said about it.

The essential points about this patient are that she developed ascites with bloody fluid, possibly a pelvic mass, occurring in a woman who was previously healthy without any history of cardiac, renal or liver disease. To my mind, that is strongly suggestive of a malignant tumor in the abdomen. However, she had missed a period recently and she had a positive test for pregnancy. Furthermore, she had not only bloody fluid in the abdomen but also a great deal of bleeding, and I presume that we have to stop and consider whether the recent pregnancy was concerned in this condition at all. I do not recall ever hearing of ascites developing in a normal intrauterine or any sort of extrauterine pregnancy. It is worth noting perhaps that the ascites began almost as soon as this hypothetical recent pregnancy, because she noticed swelling of the abdomen ten days before admission, and presumably the ascites had begun some few days before she had noticed it. The period was due two weeks before admission, but at the time she noticed the abdominal swelling she was only four days over the period and that puts the onset of ascites back to a time when she could not have been more than ten to fourteen days' pregnant. I do not believe that we need dwell on a possible pregnancy having anything to do with the ascites.

It is quite possible, of course, that she had a coincidental pregnancy. Suppose that she had a malignant abdominal tumor, with bloody ascites, and just happened to become pregnant at that time. In that case, the pregnancy would not be of any particular importance at the moment. However, there are one or two suspicious things about the case. One of them, of course, is that an obstetrician has been invited to discuss it, and it is hard to escape the feeling that we have to tie this up with pregnancy somehow. But there is another, more objective suspicion, and that is the extent of the bleeding. The woman had not only bloody fluid but also a fairly profuse intraperitoneal hemorrhage. According to the count, I should think there was a good deal more blood in the fluid than one ordinarily gets with a malignant lesion of the abdomen, such as a cancer of the ovary. This bleeding, of course, occurred after admission to the hospital — at least, the greater part of it did, because on admission she had a large, distended abdomen, but she had a normal blood pressure and pulse and the hemoglobin was 12.2 gm., which is not far below normal. What possible connection could a recent pregnancy have with this? Could a pregnancy in any way have contributed to this bleeding? Could she perhaps have had a pelvic tumor with ascites, either benign or malignant, and could the bleeding have occurred into this ascitic fluid from the pregnancy, whatever the pregnancy may have been? In that event, of course, there would have been the disadvantage of having to make two entirely separate diagnoses, which is somewhat hazardous as a rule. Furthermore, the only way that this amount of blood in the abdomen could have resulted from a pregnancy would be rupture of the uterus or an ectopic pregnancy. In the first place, the pregnancy as I pointed out earlier, was at the most four weeks along. Spontaneous rupture of a uterus with a normal intrauterine pregnancy is exceedingly rare as early as that. It does occur, but usually in the third or

fourth month. If the uterus was ruptured, one would have expected some external bleeding. Also, against either a ruptured uterus or ectopic pregnancy is the fact that the bleeding, although profuse, had apparently not been sudden. It occurred over a few days, and it did not produce pain or any symptoms of collapse, which we associate with rupture of a tubal pregnancy or rupture of a uterus. On the whole, I think we can dismiss the idea of a ruptured uterus in any sort of pregnancy.

On the other hand, one cannot get away from the fact that there was very profuse bleeding, as well as a positive Aschheim–Zondek test, and one wonders if the whole thing can be accounted for by a particular type of tumor. A chorioepithelioma will produce all these signs. It is a very rapidly growing tumor and is notorious for invading blood vessels. It could easily produce this amount of bleeding, as well as the mass in the pelvis, and could account for the positive Aschheim–Zondek test. I believe that a malignant tumor, a chorioepithelioma, is the most probable diagnosis. The possible pregnancy six months before admission is an obvious source. Whether it was a blighted ovum or a complete abortion or a pregnancy, a chorioepithelioma could still have developed in the tube or in the uterus. The fact that six months elapsed is not against that diagnosis because it is well known that there may be a long latent period between pregnancy and the development of this tumor. It is also possible, of course, for a chorioepithelioma to develop coincidentally with pregnancy, although I think it is rather unlikely that a chorioepithelioma could have developed during the past month at the onset of this hypothetical recent pregnancy. And, of course, when one gets right down to it the patient was not necessarily pregnant at all because she could have had a teratoma with chorioepitheliomatous elements in it. That is a rather farfetched diagnosis, but it has happened.

There are a number of things that would help us to confirm this diagnosis. Chorioepithelioma is well known to metastasize early and very frequently to the lung. If these pulmonary shadows on the x-ray film are consistent with metastatic tumor, I should think it would go a long way toward confirming that diagnosis. Another procedure, which was not recorded but which I am sure must have been done, is examination of the fluid for malignant cells. Then there is the question of the quantitative Aschheim–Zondek test. Perhaps that was performed. This tumor frequently metastasizes to the vagina as bluish nodules that are quite diagnostic. I do not suppose that if such nodules had been noticed they would have been included in the record — that would have made the diagnosis too easy. I think that the most important clue we can ask for is from the X-ray Department. If the presence of tumor is not confirmed, I still think that she probably had a malignant tumor, most likely a chorioepithelioma. I do not believe that one can decide where it originated, on the information we have, but one can draw certain deductions. It is quite unlikely, of course, that it was growing inside the uterus because there had been no recent uterine bleeding. It could have been an intramural nodule. In that case, the abdominal symptoms were probably due to the growth of a metastasis because had the tumor grown rapidly through the uterine wall to involve the adjacent structures, I would expect the tumor not to be freely movable and so easily felt. My guess would be, if she had a chorioepithelioma, that it probably originated outside the uterus.

Dr. Stanley M. Wyman: The masses described in the right lung are in the midlung field; the third nodule lies in the left lower-lung field. Examination about three weeks later showed the three nodules to have increased definitely in size. They have an appearance that is quite characteristic of metastatic disease. The film of the abdomen shows nothing more than probable fluid. I cannot make out a definite mass and I can see no evidence of unusual calcification.

Dr. Ellis: This patient was admitted to the hospital with a diagnosis of cirrhosis of the liver, primarily because of the ascites and the fact that nausea and vomiting played a predominant role in the symptoms in the ten days prior to admission. When she came in, it was obvious when one saw her and went into the history carefully and from the various laboratory studies that she did not have cirrhosis. Regarding Dr. Smith's questions about the period that she had six months prior to admission, the patient herself described it as a miscarriage although careful questioning did not reveal that she had actually identified the products

of the pregnancy. The specimen of the fluid was sent to the cytologic laboratory, and at the time of operation we had a telephone report that no malignant cells had been seen in it.

Clinical Diagnosis

Ovarian tumor.

Dr. Smith's Diagnosis

Chorioepithelioma, extrauterine, with pulmonary metastases.

Anatomical Diagnoses

Papillary serous adenocarcinoma.
Uterine pregnancy.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Meigs, will you tell us what you found at operation?

Dr. Joe V. Meigs: There were 3 or 4 liters of bloody fluid in the abdomen. The uterus was enlarged and was consistent with an early pregnancy. In the left ovary was an encapsulated, solid tumor, 20 cm. in diameter, which on opening was filled with dark reddish, necrotic material. The other ovary was slightly cystic. There was no evidence of metastases anywhere within the abdomen; the lymph nodes were not enlarged, and there were no papillary projections on the peritoneum. A total hysterectomy and bilateral salpingo-oophorectomy were done.

Dr. Mallory: The tumor was a solid ovarian carcinoma, with very extensive hemorrhagic necrosis of a large portion of the tumor. The cells microscopically were very anaplastic, but showed a tendency to papillary formation. The uterus disclosed a perfectly normal pregnancy in one corner, with a fetus 1.5 cm. in length.

The patient returned to the hospital four months after discharge because of epileptiform seizures, which were undoubtedly due to cerebral metastases, and died at home a few months later.

CASE 34282

Presentation of Case

A twenty-two-year-old unmarried graduate nurse was admitted to the hospital.

She had been well until nine months before entry, at which time she had an attack of fever and abdominal pain associated with prolongation of menstrual periods. At that time she was studied at another hospital, and some suspicion of paratyphoid infection was entertained but never proved. A low-grade fever persisted for several weeks and then spontaneously disappeared. Eight months before entry she had, for the first time, considerable pain with the catamenia and more profuse flowing both in amount and in duration than she had previously had. Subsequent to this, the periods were irregular, occurring every thirty-four to forty days rather than every twenty-nine days as previously. With each period she had severe lower abdominal cramps and backache. Between the periods she felt reasonably well and was able to continue her work. Five days before admission to the hospital she was examined. At that time it was found that the last menstrual period had begun nine days previously and had been extremely painful, with profuse flow, lasting for seven days. Associated with the period was a temperature as high as 101°F. The patient was unable to work and was so uncomfortable that she had to go to bed. At the time of examination the pain in the abdomen was still present although she had had no menstrual flowing for two days. Physical examination at that time showed diffuse tenderness throughout the lower abdomen, most marked in the right lower quadrant and associated with a moderate degree of resistance in the latter location. On bimanual pelvic examination the pelvic organs were not made out. There was some tenderness in the right vault; no mass was felt. The cervix was normal to inspection and to palpation. On the anterior vaginal wall there was a very tiny nodule, which seemed to be compatible with an endometrial implant. There was some tenderness also in the left vault, but not enough to interfere with the examination, and no masses were felt. Rectal examination gave no additional information. Because of persistence of the symptoms she was admitted to the hospital.

Except for an appendectomy five years before entry, the past history was irrelevant.

On physical examination no additional information was obtained.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 70 diastolic.

The urine was normal. The white-cell count was 10,700, with 53 per cent neutrophils, 1 per cent large lymphocytes, 36 per cent small lymphocytes, 8 per cent monocytes and 2 per cent eosinophils.

The red cells and platelets appeared normal. The photohemoglobin was 15.1 gm. The sedimentation rate was 0 mm. in 15 minutes, 1 mm. in 30 minutes, 1 mm. in 45 minutes, and 2 mm. in 60 minutes.

On the third hospital day a laparotomy was performed because of the persistence of abdominal pain.

Differential Diagnosis

Dr. Howard Ulfelder: This is the history of a young unmarried woman who had two attacks of abdominal pain and fever coincident with the menses. The first attack was nine months prior to admission and the second, two weeks before admission. In the interval between attacks she was well enough to work but noticed a change in the menstrual cycle; the interval increased somewhat, and she developed severe cramps, which apparently she had not had before the present illness. The fever and abdominal pain suggest to me that we are presented with either an inflammatory lesion or ischemia, although one occasionally sees tumors with fever. The location of this lesion was apparently the right lower quadrant, probably in the true pelvis because of spasm and tenderness of the right lower quadrant and some tenderness, which prevented an adequate pelvic examination. I wonder if it was unilateral in the pelvis? Certainly the majority of physical findings were on the right side, but we are told that she had some tenderness on the left side also. Is there anything that can help us localize this lesion more precisely? Were any x-ray films taken? Did she have pyelograms or a barium enema?

Dr. John B. McKittrick: No.

Dr. Ulfelder: Apparently, the gastrointestinal and the urinary tracts were not believed to be involved. There was a normal sedimentation rate and hemoglobin and an essentially normal differential count, despite elevation of the white-cell count.

Does the past history help? An appendectomy had been performed five years previously. It is conceivable that something incident to the appendectomy produced the present picture. One thinks of a foreign body, either a fecalith or some other foreign body, left at the time of appendectomy, and producing abscess in the right pelvis. I consider these unlikely, however.

Is there anything in the history to suggest pelvic inflammatory disease? We have no history of vaginal discharge or exposure to gonorrhea.

Does the character of onset of this illness suggest a complication of pregnancy? We are not told whether the bleeding with the first attack was at the expected time of menstruation or whether there had been an abnormal interval between the last normal period and the period described as occurring at the time of the original attack of pain and fever. One must consider the possibility that this patient had a pregnancy with an early miscarriage, with the retention of some products of conception and recurrent infection in the endometrium. To try to interpret the menstrual history is almost futile. The menstrual history that this patient gave may be that of anyone, including a girl who has no organic lesion.

We have been presented with the statement that she had a tiny nodule in the anterior vaginal wall, which seemed to be compatible with an endometrial implant. Endometriosis of the vaginal wall is rare. Endometriosis as an explanation of this picture in a twenty-two-year-old woman is extremely rare. I do not consider endometriosis a very strong possibility in this patient.

To summarize, it is my opinion that this patient was suffering from a lesion in the right pelvis connected with the genital tract, which was either inflammatory or ischemic in character. Foreign body is a possibility; I do not consider it very seriously. Pelvic inflammatory disease is a strong possibility. I have mentioned the possibility of a retained placental fragment; that must be considered. Tuberculosis, lymphoma or congenital anomaly might explain the picture. The congenital anomaly that I have in mind, as a possible but not a likely explanation, is a double uterus with a very small uterus on the right side and a normal one on the left side, with some obstruction in the canal from the small right-sided uterus. I do not consider it seriously but merely mention it.

My belief is that this patient suffered from a lesion that was primarily ischemic and recurrent, and, therefore, I believe that a cyst of the right ovary with torsion is the most likely diagnosis. I had hoped an x-ray film might help in deciding whether or not a cyst was present, and if present, whether it contained calcification. The lesion seemed to be anterior, in that the patient had

spasm and tenderness in the right lower quadrant, and this suggests a dermoid rather than a follicular cyst. I shall make a diagnosis of twisted dermoid cyst of the right ovary.

Dr. Benjamin Castleman: The preoperative diagnosis that Dr. Leland S. McKittrick made was "pelvic pain, cause undetermined." Can you tell us about the operation, Dr. McKittrick?

Dr. John B. McKittrick: This patient was seen by several doctors, who were unable to make a more accurate diagnosis. The question of pregnancy or pelvic inflammatory disease was raised, but there was no reasonable evidence for such a diagnosis. She had no vaginal discharge. The cervix was perfectly normal; there was no suggestion of pelvic inflammatory disease either clinically or by physical examination. Physical examination was difficult because of the mechanical situation. She was very large, with an extremely difficult pelvis to examine purely because of the size. Even under ether it was not easy to determine what was in the pelvis. We approached the situation with no diagnosis except excruciating pelvic pain.

Clinical Diagnosis

Pelvic pain, cause undetermined.

Dr. Ulfelder's Diagnosis

Twisted dermoid cyst of ovary.

Anatomical Diagnosis

Tuberculous salpingitis and endometritis.

Pathological Discussion

Dr. McKittrick: At the time of operation we were surprised to find that both tubes were involved in the process. The left was worse than the right. It was swollen, and the fimbriated end obliterated. The tube was nodular throughout. The right tube was obstructed just proximal to the fimbriated end and was nodular but less swollen and thickened than the left tube. Over the anterior surface of the uterus were multiple, white, miliary nodules. Our gross diagnosis at operation was tuberculosis. A curettage had been performed preliminary to laparotomy, but very little tissue was obtained and nothing characteristic was determined on appearance. The diagnosis of tuberculosis was subsequently confirmed grossly by Dr. Castleman, who saw the patient in the operating room.

We removed a portion of the left tube for a biopsy. Elsewhere in the peritoneal cavity there was no evidence of disease. After much discussion it was decided not to do anything more surgically and to send the patient to a sanatorium.

Dr. Castleman: Our permanent microscopical sections showed an active tuberculous process not only in the tube but also in the endometrium.

Dr. McKittrick: Within two months after arrival at the sanatorium, the symptoms became so severe and persistent that it was thought advisable to do a hysterectomy. At the time of the second operation the disease had spread although the ovaries were not involved. A supravaginal hysterectomy was done. The patient remained well for about two months after the laparotomy and then had a recurrence of severe, excruciating pain, with profuse discharge from the vagina, and later developed urinary symptoms. I think it was established that the vaginal discharge was caused by tuberculosis, but the urinary-tract disease was never, to my knowledge, proved to be tuberculosis. She was treated with streptomycin for three months, but it was stopped when she developed severe vertigo. I have not heard from her recently, but ten months after the operation she was still having a difficult time, still having pain and profuse discharge. For a while the streptomycin slowed up the discharge. I do not know what the course was from that time on. Dr. King saw the patient. It would be interesting to hear what he has to say.

Dr. Donald S. King: I saw her after her first operation and found no active pulmonary tuberculosis.

Dr. McKittrick: We looked hard for generalized tuberculosis but found none whatsoever.

Dr. Castleman: Do you think that the entire uterus should have been taken out?

Dr. Ulfelder: In retrospect, there is no question that she had tuberculosis of the cervix, which accounted for the continued vaginal discharge.

A Physician: I saw this patient two days ago, which is just about two years since she was in this hospital. She now has a vesicovaginal fistula, and they are finding tubercle bacilli in the urine on each examination. There is some discussion now about taking out the kidney. It is a rather stormy outlook.

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SMALLPOX TO TETANUS: A HUNDRED AND FIFTY YEARS OF IMMUNIZATION

THE value of vaccination against smallpox cannot be questioned, but now, a century and a half after its effectiveness was clearly shown, vaccination is still by no means universally employed, even in certain enlightened areas in the United States. There are protests against its use from those who either cannot or will not see its merit. In earlier years the slowness of its adoption could be explained, in part, by the lack of efficient methods of demonstrating the good results to the public. Also, in the early stages of its use no really large-scale and well controlled figures were possible.

Today, with present methods of broadcasting knowledge, scientific and otherwise, no excuse can be offered for failure to recognize the benefits of immunization against tetanus. The now tabulated results of not thousands, but millions, of cases in the armed forces all over the world furnish conclusive evidence of the efficacy of immunization against tetanus. The procedure is simple, safe and relatively painless. The results admit of no argument regarding its effectiveness, as amply demonstrated by Press elsewhere in this issue of the *Journal*.

Scarcely a day goes by in which a physician does not see a case in which tetanus could result from a minor wound. In the days when tetanus antitoxin was his only recourse he was constantly obliged to make the important and sometimes difficult decision whether the patient should be subjected to such serum therapy, with its discomforts and its dangers, or whether by withholding it, to obviate these discomforts at the risk of the disease. Such a difficulty is no longer necessary.

There are, of course, those who protest against any and all progress in medicine. As there are conscientious objectors to vaccination against smallpox, so there are inevitably those who would object to any advance, even though the known facts of its efficacy permitted of no dispute.

It is most desirable, therefore, that general practitioners do what they can, and as much as they can, to promote the acceptance by the public of active immunization against tetanus. Tetanus toxoid will protect the individual person, and its universal use may greatly ease the burdens of the physician.

SYRINGE-TRANSMITTED HEPATITIS

THE occurrence of a severe form of hepatitis often referred to as "homologous serum jaundice" following injections of normal or immune plasma, serum or whole blood or after inoculations of certain vaccines containing normal serum or plasma is now well recognized. This type of hepatitis was observed in widespread epidemics in military

personnel during the war and has also occurred not infrequently in civilian practice.

Attention is now being focused on a new mode of transmission of this serious form of hepatitis — namely, by means of the unsterile or inadequately sterilized needle or syringe. British workers have called attention to the frequent occurrence of such transmission during the treatment of syphilitic patients, in whom it is considered to be the chief cause of the so-called arsphenamine hepatitis.[1, 2] It has also been implicated as a possible cause of an outbreak of hepatitis in a diabetic clinic[3] and as the cause of similar illnesses in patients who are under treatment with penicillin for a variety of diseases.[4-6] Furthermore, infectious hepatitis can be transmitted from one patient to another by syringes used for the collection of blood,[7] and this was probably the mode of transmission in the diabetic clinic.

The syringe transmission of hepatitis is made possible by the fact that very little blood or serum of an infected carrier is necessary to transmit the disease and also by the fact that the causative virus is a hardy one that resists the cursory types of sterilization that are often practiced in busy clinics in which numerous blood samples are drawn or many injections have to be given in a short time. Mendelssohn and Witts[8] showed that during an ordinary venipuncture some of the blood is sucked back from the syringe when the tourniquet is released, and this permits infected materials previously present in the syringe or needle to enter the blood stream of the patient whose blood is being drawn. It has also been demonstrated that during the course of an injection, some blood or serum from the patient may be forced up through the needle during the contraction of the recipient's muscle, thus resulting in contamination of the syringe.

Capps, Sborov and Scheiffley[9] have recently reported an epidemic of infectious hepatitis apparently resulting from the use of the "multiple dose per syringe" for the administration of tetanus toxoid. In this outbreak 20 per cent of the recipients of the toxoid contracted acute infectious hepatitis. It was estimated that about five per cent of the original group of people being vaccinated must have carried the hepatitis virus in their blood, and it is believed that the syringes became contaminated with the blood from these persons, before all the toxoid had been dispensed. Although separate needles were used for subsequent inoculations of the toxoid from these syringes, a large proportion of those receiving the later injections were inoculated with the virus and thus later came down with the hepatitis.

The implications of these findings are obvious. Modern medical practice involves considerable use of needles and syringes for bloodletting and also for various types of injections. These facts and the tremendous development of the use of whole blood and blood products and the general system of blood banks being established in this country all point to the importance of this mode of transmitting such a serious disease. From the point of view of syringe transmission the significance of adequate sterilization is obvious. This can be accomplished by dry heat sterilization, autoclaving or boiling for about thirty minutes and the use of individual, sterile needles and syringes for every puncture. The need for adequate supplies of needles and syringes in large clinics or when many injections must be given also becomes apparent.

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THE LEADING CAUSES OF DEATH

The mortality statistics recently presented by the United States Public Health Service,[1] indicating "a new record low" for the crude death rate in the United States in 1946, underline the fact that these data should be interpreted with caution; the equivocal significance of such figures has previously been

referred to in these columns.[2] And the decline in the number of deaths from certain leading causes should be balanced against the increase in other fatal diseases. Thus, although the deaths from intracranial lesions of vascular origin and from nephritis decreased, respectively, from 129,144 and 88,078 in 1945 to 125,649 and 81,701 in 1946, the deaths from cancer increased from 177,464 in 1945 to 182,000 in 1946, and those from heart disease from 424,328 to 429,230. One class of preventable deaths (those due to accidents), which rose from 95,918 in 1945 to 98,033 in 1946, remains both a challenge and a disgrace to a nation in which a great part of private and public-health medical practice is devoted to the prolongation of life.

Cancer and other malignant tumors continue to take a large toll, accounting for 13 per cent of the total number of deaths in 1946. Although he admits the uncomfortable implications of such a figure, Johnson[3] points out some hopeful trends. The rate of deaths from cancer at all ages rose from 60 per 100,000 population in 1900 to 130 per 100,000 in 1940, but this depressing figure should be considered in the light of the 67 per cent increase in the age group over forty-five years, in which the greatest incidence of cancer occurs. And although the number of deaths from cancer of the respiratory tract continues to rise each year, deaths due to malignant lesions of the skin, mouth, stomach and liver have steadily decreased in the last twelve years — Johnson suggests an interesting causal relation between the decline in the death rate from gastric cancer and the fact that the decrease began approximately twenty-five years after significant changes in the dietary habits of the American people had taken place.

Despite the truly remarkable advances in the control of disease and the prolongation of life, science has not succeeded in making man immortal. Johnson[3] questions whether it is desirable to concentrate on that goal alone. He expresses what should be a major consideration in the relatively new field of geriatrics, "the enrichment of living rather than the mere prolongation of life." There is no indication for congratulations in the vital statistics referred to above: the five leading causes of death, whether they are the causes at present responsible or others that will take their place, will continue to exact their yearly toll, particularly among the elderly. And medical science will continue its campaign not only, by control of the diseases that cause most deaths, to extend the span of life but also to eliminate the physiologic discomforts that plague old age — in short, to avoid a "second age of dependency"[4] and make of old age a period of dignity and mental and physical well-being.

References

1. U. S. Public Health Service, National Office of Vital Statistics. Mimeographed memorandum, dated December 30, 1947.
2. Editorial. Fallacy of crude death rate. *New Eng. J. Med.* **238**:577, 1948.
3. Johnson, A. S. Annual Oration: Medicine's responsibility in propagation of poor protoplasm. *New Eng. J. Med.* **238**:755-758, 1948.
4. Editorial. Second age of dependency. *New Eng. J. Med.* **238**:340, 1948.

LION ROARS LESS LOUDLY

The Comitia of the Royal College of Physicians, acting in a spirit of sweet reasonableness, has forwarded two resolutions to the minister of health, Aneurin Bevan, vociferous sponsor of the National Health Service Act of 1946. The first suggests that an act be brought in by the minister of health amending the National Health Service Act of 1946 by discarding full-time medical service by regulation. The second recommends a bill to make regulations affecting the National Health Service subject to special parliamentary procedure rather than to ministerial dictation alone.

Mr. Bevan, departing from his accustomed role, has apparently listened to the voice of the British Medical Association as expressed in its plebiscite of January 31, in which it overwhelmingly rejected the National Health Service Act as it was originally written.

He has now proposed his own modifications of the Act. In these he relinquishes a full-time service to be brought into effect by regulation and also modifies the proposal for a universal basic salary, limiting such salaries to three years, after which the practitioner may make his own decision whether to continue with salary and capitation fee, or to continue with a capitation fee as the sole source of income from practice.

These new proposals represent a considerable willingness to compromise, since even his own party is not entirely in sympathy with them.

The Government, according to Mr. Bevan's parliamentary secretary, now recognizes that a full-time salaried service is incompatible with free choice of physician by the patient; more, it recognizes the importance of the principle of free choice of physician and therefore puts forward the compromise of payment partly by capitation fee and partly by salary. Further, although the buying and selling of public practices will still be forbidden, every doctor will be free to practice where he wishes, except in professionally overcrowded areas, and will have the right to choose his partner or assistant.

A few strands of democracy will remain in Britain's anchor line, although, as the *British Medical Journal** phrases it, "Mr. Bevan's machinery may provide that justice will be done, but we doubt whether it will make it possible that justice 'may manifestly be seen to be done.' "

A plebiscite on the amendments proposed by the Government indicates that approximately 64 per cent of the British Medical Association members still disapprove of the Act, with 36 per cent approving. Only 52 per cent, however, are against serving under the Act whether they like it or not, a majority so bare that further organized resistance seems impossible.

There is no question that, with Britain's peculiar genius for compromise, the doctors of England will now unite in an organized effort to make the new system effective.

*Editorial. Plebiscite. *Brit. M. J.* **1**: 791-793, 1948.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Flagg — Elisha Flagg, M.D., of Boston, died on June 8. He was in his eighty-third year.

Dr. Flagg received his degree from Harvard Medical School in 1901. He was formerly treasurer of the Boston Medical Library.

His widow, a daughter and two grandchildren survive.

Small — Albert E. Small, M.D., of Melrose, died on June 9. He was in his seventy-third year.

Dr. Small received his degree from Harvard Medical School in 1900. He was formerly president, secretary and treasurer of Middlesex East District Medical Society, and was chairman of the Melrose Board of Health. He was a fellow of the American Medical Association.

Two children survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1948

Résumé

Diseases	May 1948	May 1947	Seven-Year Median
Chancroid	2	0	2*
Chicken-pox	1612	2599	1763
Diphtheria	18	37	16
Dog bite	1260	1232	1289
Dysentery, bacillary	8	5	5
German measles	132	107	640
Gonorrhea	218	273	340
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	2	0	2*
Malaria	1	10	12
Measles	5743	1783	4208
Meningitis, meningococcal	7	3	16
Meningitis, Pfeiffer-bacillus	4	10	2
Meningitis, pneumococcal	2	2	5†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	1	0	2†
Meningitis, other forms	2	0	1†
Meningitis, undetermined	3	4	4†
Mumps	2404	1095	1459
Pneumonia, lobar	70	173	210
Poliomyelitis	0	0	1
Salmonellosis	6	14	6
Scarlet fever	910	440	1120
Syphilis	182	279	439
Tuberculosis, pulmonary	224	248	303
Tuberculosis, other forms	13	22	23
Typhoid fever	5	1	2
Undulant fever	4	8	6
Whooping cough	134	495	573

*Four-year median.
†Six-year median.

Comment

Diseases with incidence above the seven-year median were diphtheria, bacillary dysentery, measles, mumps and typhoid fever.

Diseases with an incidence below the seven-year median were chicken pox, German measles, malaria, meningitis, all forms, lobar pneumonia, scarlet fever, undulant fever and whooping cough.

Mumps had the highest incidence since 1915. There were more cases of typhoid fever in May than in the last six years. Whooping cough and lobar pneumonia were at the lowest level since 1915.

Geographic Distribution of Certain Diseases

Diphtheria was reported from: Boston, 7; Brockton, 4; Chelsea, 1; Everett, 1; East Bridgewater, 1; Peabody, 1; Somerville, 1; Watertown, 2; total, 18.

Dysentery, bacillary, was reported from: Waltham, 1; Worcester, 7; total, 8.

Encephalitis, infectious, was reported from: Cambridge, 2; Fitchburg, 1; Lowell, 1; Waltham, 1; total, 5.

Malaria was reported from: Boston, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 2; Everett, 1; Lynn, 1; Medford, 1; Newton, 1; Quincy, 1; total, 7.

Meningitis, Pfeiffer-bacillus, was reported from: Acton, 1; Lowell, 1; New Bedford, 2; total, 4.

Meningitis, pneumococcal, was reported from: Brookline, 1; Tewksbury, 1; total, 2.

Meningitis, streptococcal, was reported from: Cambridge, 1; total, 1.

Meningitis, other forms, was reported from: Boston, 1; Reading, 1; total, 2.

Meningitis, undetermined, was reported from: Braintree, 1; Newton, 1; Worcester, 1; total, 3.

Salmonellosis was reported from: Beverly, 3; Boston, 1; Haverhill, 1; Otis, 1; total, 6.

Septic sore throat was reported from: Boston, 7: Medford, 1; Milton, 1; total, 9.

Tetanus was reported from: Worcester, 1; total, 1.

Typhoid fever was reported from: Boston, 3; New Bedford, 1; Westfield, 1; total, 5.

Undulant fever was reported from: Easton, 1; Hopkinton, 1; Newton, 1; Webster, 1; total, 4.

CORRESPONDENCE

COUNCY AND THE ASSOCIATION OF AMERICAN PHYSICIANS

To the Editor: The editorial, "Four Hundred and Thirty Years Ago," in the May 20 issue of the *Journal*, which I read with interest, contains a minor error, perhaps of no importance to anybody, but I think you might like to know about it. That concerns the Association of American Physicians and Dr. Councilman. I am sure that Dr. Councilman had very little to do with the founding of the Association of American Physicians, although he was one of sixty-nine original members. The reason I say that is that Dr. Councilman then was only eight years out of medical school, was an associate in pathology at the Johns Hopkins Hospital with Dr. Welch, beginning at a time when the hospital had not been built.

The editorial also states that he was known as "Councy." I never heard this term used. He was affectionately spoken of by the younger men as "Counce" and was known as "Counce" to many of his colleagues. Dr. Welch, of course, was always known to the younger men as "Popsy," though I never heard anyone call him that. He was always known as Dr. Welch, Welch, to a very few as William and to an occasional member of his family as Willie. I never knew who designated him first as Popsy. When I went to Johns Hopkins in the autumn of 1896 he was universally spoken of by the students as Popsy.

HENRY A. CHRISTIAN

Brookline

Note: Dr. Councilman was later known to his students at Harvard Medical School as "Councy." — ED.

BOOK REVIEW

Surgical Treatment of the Abdomen. Supervising editor: Frederic W. Bancroft, M.D. Associate editor: Preston A. Wade, M.D. 4°, cloth, 1026 pp., with 457 illustrations and 3 color plates. Philadelphia: J. B. Lippincott Company, 1947. $18.00.

This comprehensive and authoritative volume was written by thirty-five eminent physicians. The scope of the book is sufficiently broad to comprise a thorough consideration of fundamental surgical principles applicable to the exacting requirements of gastrointestinal surgery. Adequate coverage is given to the common problems of anesthesia, preoperative and postoperative care and the essential features of a sound surgical technic. The sections relating to the various diseases involving the gastrointestinal tract are well documented and generously illustrated.

The chapter pertaining to the surgical lesions of the small bowel is particularly noteworthy in terms of its broad scope, its ample pictorial documentation and its careful presentation of the controversial aspects of the surgical management of lesions of the small intestine.

Each section, by and large, achieves the purpose of portraying the dominant clinical features of the diseases that are discussed—the diagnosis, an acceptable method of surgical management and a reasonable consideration of the results that can be achieved by the proposed methods of therapy.

Although one might question the urgent need for such a volume, no one could question its authoritativeness or its essential soundness.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Atlas of Practical Incisions and Some Operative Procedures. By Oliver C. Cox, M.D. 4°, cloth, 85 pp., with 27 illustrations and 61 plates. With drawings by Garnet W. Jex, and photographs by John W. McGuire. Baltimore: Williams and Wilkins Company, 1947. $3.00.

In this atlas the author presents incisions recommended for various surgical operations on the gall bladder, appendix, undescended testicle, hernia and pilonidal cyst, and considers the "reverse" Pfannenstiel and the Parker–Kerr aseptic enteroenterostomy. The plates are excellent and self-explanatory. There are short comments with each series of incisions, but otherwise there is no text. The volume is well published and should prove useful to students and beginners in surgery.

George Crile: An autobiography. Edited, with sidelights, by Grace Crile. In two volumes. 8°, cloth, Vol. I, 306 pp., Vol. II, 317 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1947. $10.00.

The material for this autobiography of a celebrated physician scientist was compiled from the notes, letters, diaries and manuscripts of Dr. Crile, who also wrote the material for the early chapters, until his vision became impaired. Here will be found the history of his work on surgical shock, fear, blood pressure, surgery of the respiratory system, hemorrhage and transfusion, the thyroid gland, anemia and resuscitation, phylogenetic association, anoci-association, the emotions, kinetic drive and the bipolar theory. Dr. Crile made a life-long study of surgical shock and perfected a shockless operating technic. He performed the first successful amputation under local anesthesia in 1897 and the first successful blood transfusion in 1906. He perfected the nitrous oxide method of general anesthesia. He was a motivating force in the founding of the American College of Surgeons and the American Society of Clinical Research. Prior to World War I he set up an ambulance service in Paris and organized Red Cross Base Hospital Units; later he was a member of the first contingent of the United States Army to serve overseas in the war, establishing a hospital at Rouen in 1917 before the arrival of troops. At the end of the war he was director of medical research for the Army. Returning to Cleveland he was instrumental in building and operating the Lakeside Clinic, which pioneered in radiotherapy and biophysics. Dr. Crile was a traveler. He made two European trips previous to his marriage and upon that occasion made a global trip. During the later years he made numerous trips to Europe, Africa, Alaska, California and Florida to study the endocrine functions of the larger animals and marine life. For this and other work he received many honors including the Lannelongue surgical medal of the Surgical Society of Paris. This work should be in all medical-history collections.

Hypnotherapy: A survey of the literature. By Margaret Brenman, Ph.D., director, Division of Psychology, The Menninger Foundation, and professor of psychology, The Menninger Foundation Center of the Department of Psychology, University of Kansas; and Merton M. Gill, M.D., associate psychiatrist and assistant director, Department of Research, The Menninger Foundation. With appended case reports and an experimental study. 8°. cloth, 276 pp. New York: International Universities Press, 1947. $4.50. The Menninger Foundation Monograph Series No. 5.

This work was orginally published by the Josiah Macy, Jr., Foundation in 1944, and distributed to psychiatrists and psychologists as part of its wartime services. It is reissued in a commercial edition with two new appendixes. The general bibliography lists 295 sources comprising the basis of the survey. The text is divided into six parts and two appendixes. The first part is a short sketch on the historical development of hypnotherapy, followed by methods of inducing and terminating hypnosis; susceptibility of hypnosis; therapeutic applications; the theory of hypnosis; and a summary and statement of problems. The first appendix discusses in detail 4 unusual cases of anxiety hysteria; hysterical psychosis in a seventy-one-year-old woman; a case of combined neurasthenia, hysteria and depression; and a case of neurosis in a young girl, illustrating the technics of hypnotherapy, hypnoanalysis and psychoanalysis. Seventy pages of text are devoted to these cases. The second appendix is devoted to a discussion of the use of hypnotic technics in the study of tension systems, giving in detail accounts of the experiments used in the study. There are special bibliographies for the case reports and for the experimental study. The volume is well published, with a good type on good light paper. The work should be in all collections on psychiatry.

(*Notices on page xv*)